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Associated malignant neoplasms in patients diagnosed with tumours of haematopoietic and lymphoid tissues: a retrospective population-based study in the Canton of Zurich

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1 Abbreviations

AILT	Angioimmunoblastic T cell lymphoma
ALL	Acute lymphocytic leukaemia
AML	Acute myeloid leukaemia
AMN	Associated malignant neoplasm
CLL	Chronic lymphoid leukaemia
CML	Chronic myeloid leukaemia
DLBL	Diffuse large B cell lymphoma
EBV	Epstein-Barr virus
FL	Follicular lymphoma
HCL	Hairy cell leukaemia
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HPSCD	Haematopoietic stem cell disease
LBL	Lymphoblastic lymphoma
LDHL	Lymphocyte depleted Hodgkin lymphoma
LPL	Lymphoplasmacytic lymphoma
MCHL	Mixed cellularity Hodgkin lymphoma
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndrome
MM	Multiple myeloma
MPD	Myeloproliferative disease
NHL	Non Hodgkin lymphoma
NLPHL	Nodular lymphocyte predominant Hodgkin lymphoma
NOS	Not otherwise specified
NSHL	Nodular sclerosis Hodgkin lymphoma
RR	Relative risk
SIR	Standardized incidence ratio
SLL	Small cell lymphocytic lymphoma
SMN	Second malignant neoplasm

Table 1: Abbreviations (in alphabetic order)

2 Summary

2.1 Introduction

Numerous studies document that lymphoid and haematopoietic tumours and their therapy increase the risk of second malignant neoplasms [1]-[22]. The reverse, a study of the incidence of lymphoid and haematological tumours after a diagnosis of solid cancer has rarely been performed [23]. We undertook this study to analyse the incidence of associated neoplasms preceding and following the diagnosis of cancers of lymphoid and haematopoietic tissues.

2.2 Materials and Methods

The data of the cancer registry of the Canton of Zurich (population of 1.3 million) was our source. 12'798 patients with one or more than one cancer of haematopoietic and lymphoid tissues, had been recorded between January 1980 to June 2008.

2.3 Results

In total we detected 2'885 previous and subsequent associated malignant neoplasms (AMN) in 12'798 patients. In the order of descending frequency, 433 cancers of prostate, 354 cancers of breast, 295 cancers of colorectum and 227 cancers of lung were detected. After excluding patients with more than one cancer of haematopoietic and lymphoid tissues, we detected 2'374 previous and subsequent AMN in 10'923 patients.
205 in 1'000 lymphohaematopoetic cancers are associated with another cancer. Solid and non solid AMN were mostly associated with indolent B cell lymphomas and Hodgkin lymphomas (HL) (237/1'000 cases for both).
Statistical analyses showed a most significant increase of AMN as before and after HL. Statistical analyses using a generalized additive model for Poisson regression confirmed this increase. AMN among HL patients were mostly cancer of breast, bronchus and lung, prostate and colorectum.
Up to 25% of women with HL diagnosed between 20 and 30 years old developed a previous or subsequent solid cancer in the study period from 1980 and 2008. Almost 30% of women with HL diagnosed between 65 and 74 years old had a previous solid AMN in the study period from 1980 and 2008. Particulary 17% of women with HL diagnosed between 65 and 69 years old had a previous cancer of breast in the study period from 1980 and 2008 (versus 4% in all women with tumours of haematopoietic and lymphoid tissues diagnosed between 65 and 69 years old).
The relative risk (RR) of previous solid malignant neoplasm in HL patients compared to patients with all other tumours of haematopoietic and lymphoid tissues (except HL) diagnosed between 65 and 69 years old is 2,29 among women and 1,31 among men. The RR of previous breast cancer in HL patients compared to patients with all other tumours of haematopoietic and lymphoid tissues (except HL) diagnosed between 65 and 69 years old is 3,80.

2.4 Conclusion

In this population-based study we could show that HL that occurred early in life, are associated with later malignancies. But HL are also associated with previous malignant neoplasms including breast, lung, prostate and colorectum cancers when HL occur later in life. The reason for this association of previous malignant tumours with later HL may include common genetic risk factors, direct genotoxic therapy effects and immunomodulation due to therapy or due to the cancer itself.

3 Introduction

3.1 Definition and classification of tumours of haematopoietic and lymphoid tissues

3.1.1 WHO classification

Neoplasms originating in the haematopoietic and lymphoid tissues consist of several closely related groups of neoplasms. The World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues [24]. renewed in 2008 is based on a biological classification. Unlike the epidemiologic taxonomy used in numerous epidemiological studies, this classification classifies neoplasms primarily according to their lineage (e.g. myeloid or lymphoid origin) [24].

3.1.2 Subdivisions in categories

Haematopoietic and lymphoid tumours are subdivided into 6 groups according to their morphology, immunophenotype, genetic and clinical characteristics: chronic myeloproliferative diseases, myelodysplastic syndromes, acute myeloid and lymphoid leukaemias, neoplasms of mature B cell, Hodgkin lymphomas and T cell/natural killer cell neoplasms [24].

3.2 Incidences of tumours of haematopoietic and lymphoid tissues

3.2.1 Geographic incidence

In 2006 the fraction of non Hodgkin lymphoma (NHL) in Western Europe (European economic area and Switzerland) represented 3.2% of all cancers (74'800 cases of NHL). The fraction of leukaemia represented 2.6% of all cancers (61'400 cases of leukaemias) [25].
From 1985 to 2004 50’066 new cases of lymphoid and haematopoietic tumours have been reported in Switzerland. On average, 2’503 new cases have been diagnosed per year [26].

3.2.2 Age specific incidence

The incidence of NHL typically increases exponentially with the average age of diagnosis. In contrast, the incidence of HL shows typically two peaks depending on age: the first peak between the age of 20 and 25 years and the second peak between 75 and 80 years [27]. In Switzerland (1993-2004), 68% of HL are diagnosed between 0-49 years of age. NHL, multiple myelomas (MM) and leukaemias are diagnosed mostly in patients over 70 years old (>70 years: 45% of NHL, 57% of MM and 46% of leukaemias) [26].

3.2.3 Gender specific incidence

Lymphoid and haematopoietic tumours occur more frequently in the male population [27].

3.2.4 Trends in incidence

A steady increase has been observed over the last decades in almost all haematopoietic and lymphoid neoplasms [28]. The reason for this trend is unknown. The occurrence of HIV associated-NHL in the 1980's only partially explains this increase [29].

3.2.5 Incidence variations between subtypes

Furthermore the incidence, average age at diagnosis and sex ratio vary between different types of lymphoid and haematopoietic tumours. This has been suggested to be due to different etiological factors [28][30].
These etiological factors include genetic factors, immunosuppression, infections, medical therapy as well as lifestyle and occupational exposures.

3.3 *Etiologies of tumours of haematopoietic and lymphoid tissues*

3.3.1 Genetic factor and tumours of haematopoietic and lymphoid tissues

The most commonly described mutations associated with tumours of haematopoietic and lymphoid tissues are:

- t (14;18) chromosomal translocation associated with follicular lymphoma (FL) [31]
- t (8;14) chromosomal translocation associated with Burkitt's lymphoma [31]
- t (11;14) chromosomal translocation associated with mantle cell lymphoma (MCL) [32]
- t (9;22) chromosomal translocation associated with chronic myeloid leukaemia (CML) [31]
- trisomy 12 associated with small lymphocytic lymphoma (SLL) [31].

In addition to spontaneous translocations, mutations secondary to viral infection and ionizing radiation can contribute to the formation of genetic mutations [33].

A familial increased risk has been observed for HL. A higher incidence is mostly seen in twins and siblings of HL patients diagnosed before the age of 50. A genetic susceptibility to HL could be attributed to HLA locus [29]. In comparison the risk of NHL is only modestly increased in follow-up of first-degree relatives of patients with NHL [29]. There is evidence of chronic lymphoid leukaemia (CLL) running in families (especially in first degree relatives) but most cases do not have a familial link [34].

Certain inherited conditions, such as Fanconi anaemia can increase the risk of developing acute myeloid leukaemia (AML). Children with Down's syndrome are more likely to suffer from AML than other children [34].

Some specific germline mutations are associated with tumours of haematopoietic and lymphoid tissues and other type of cancers. For example the germline mutation in the p53 tumour suppressor gene, as in Li-Fraumeni syndrome, is associated with breast cancers, soft tissue sarcomas, osteosarcomas, brain tumors, acute leukaemias and adrenocortical tumours [35].

3.3.2 Lifestyle and occupational exposure and tumours of haematopoietic and lymphoid tissues

Pesticides, hair dyes, tobacco use, alcohol consumption and sun exposure have been proposed to contribute to the occurrence of NHL [33][36].

The role of tobacco and UV radiation is controversial. In a few cohort studies, smoking was linked to high-grade NHL and FL [31]. Many studies have shown controversial correlation between NHL and UV radiation that may be due to its immunosuppressive effect [37].

Longtime occupational exposure to benzene increases the risk of acute leukaemias (ALL, CML and AML) [34]. An increased overall lymphoma risk has been observed among architects, maids, farmers, glass formers and construction workers. In the occupational group analyses of lymphoma subentities, HL is only significantly associated with rubber and plastic products making. Diffuse large B cell lymphoma (DLBL) risk is considerably increased among metal processors. Several occupational groups (medical, dental, and veterinary workers; sales workers; machinery fitters; and electrical fitters) showed an highly significant increased risk of FL. Farmers as well as agriculture and animal husbandry workers showed a particularly increased risk of MM [38].

3.3.3 Altered immunological function and tumours of haematopoietic and lymphoid tissues

3.3.3.1 Primary and congenital immunodeficiencies

Evidence suggests that altered immunological function, either immunostimulation or immunosuppression can be responsible for an increased risk of lymphoma [36].
The immunosuppression can be due to a primary congenital immunodeficiency or an acquired immunodeficiency such as those encountered as side effects of immunosuppressive therapies, complications following certain chronic diseases or cancers, particularly tumours of haematopoietic and lymphoid tissues [29].

Primary congenital immunodeficiencies caused by congenital X-linked immunodeficiency, ataxia-telangiectasia and Wiskott–Aldrich syndrome are associated with NHL. NHL represents one-to two-thirds of all cancers in this population [29][31].

3.3.3.2 Secondary and acquired immunosuppressions

Acquired immunosuppression such as caused by auto-immune disease or immunosuppressive therapy is associated with an increased risk of NHL [29].
Patients with rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s syndrome and celiac disease have been found to also have an increased risk of NHL [29][33][37].
Increased NHL occurrence has been described among patients treated with immunosuppressive drugs (such as cyclosporin and azathioprine) following kidney, heart and bone marrow transplantation [29][31]. The literature also shows an increased risk of developing HL after allogenic bone marrow transplantation [29].

3.3.4 Infection and tumours of haematopoietic and lymphoid tissues

NHL is 80 times more frequent among HIV positive patients worldwide than in the general population. About 4% of symptomatic HIV positive patients develop a NHL each year [36]. Epstein-Barr virus (EBV) can be detected within about 40% of NHL patients with AIDS [29].

EBV is associated with HL and NHL, specially Burkitt's lymphoma in endemic areas. HL and NHL other than Burkitt's lymphoma are associated with EBV and immunosuppression [36].

Hepatitis C virus (HCV) and human herpes virus 8 (HHV 8) have also been linked to the development of NHL [36].

Helicobacter pylori is a confirmed risk factor for gastric NHL, namely MALT lymphoma [36].

Finally human T-cell lymphotropic virus type 1 (HTLV-1), endemic in southern Japan, in the Caribbean and in Africa, causes a rare type of T-cell-leukaemia [36].

3.3.5 Therapy and tumours of haematopoietic and lymphoid tissues

In comparison with other malignancies, some evidence suggests that the risk of NHL and HL is not considerably increased by exposure to ionizing radiation [32]. On the opposite, high levels of radiation increases the risk of acute leukaemia. Indeed people exposed to the atomic bomb explosions in Japan had higher rates of myeloid leukaemias [34].

Exposure to alkylating agents (melphalan and nitrogen mustard) and type II topoisomerase inhibitors (etoposide and teniposide) during chemotherapy has been implicated in the development of myeloid leukaemia [32].

3.4 Conceptual scheme of associated cancers in patients with tumours of haematopoietic and lymphoid tissues

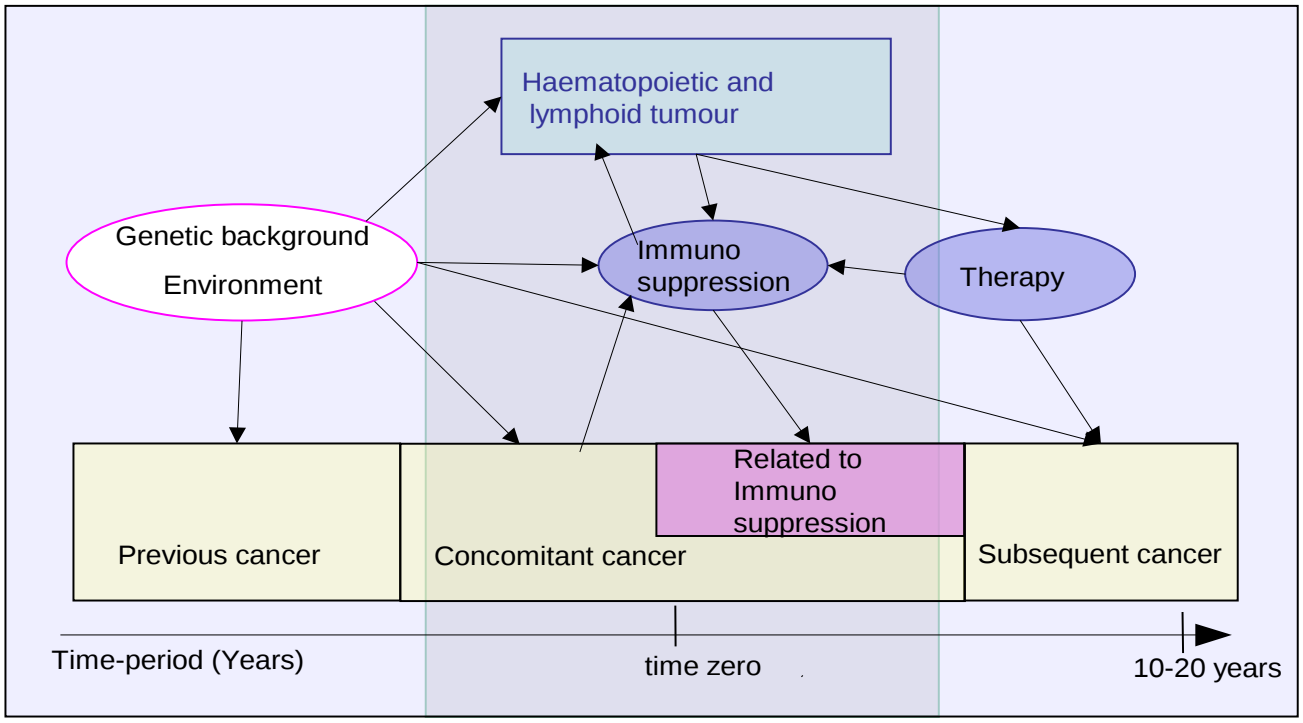


Figure 1: Conceptual scheme of associated cancers and tumours of haematopoietic and lymphoid tissues

Figure 1 shows the conceptual scheme of associated cancers and tumours of haematopoietic and lymphoid tissues. Common genetic and environmental factors can induce two concomitant cancers, but also an associated cancer before or after a tumour of haematopoietic and lymphoid tissue. Furthermore haematopoietic and lymphoid neoplasms and their therapies can result in immunosuppression, which can secondarily be more permissive for an associated cancer. Therapy alone can also directly induce the development of an associated cancer.

3.5 Secondary cancers in the population of lymphoid and haematopoietic cancer patients in the literature

3.5.1 Secondary cancer after a first malignant neoplasm

Many studies have analysed the general risk of developing a secondary malignant neoplasm (SMN) after a first malignant neoplasm [39][40][41].

The cumulative risk of developing a second cancer after a first malignant neoplasm varies between 2.6% and 5% after 20 years of follow-up [39][40][41].

High rates of secondary cancer have been observed among patients with an initial tumour diagnosis of retinoblastoma or malignant lymphoma (mostly HL). Several other types of tumours like leukaemia, soft-tissue sarcoma and Wilms' tumour showed likewise an increased risk of developing a SMN [39][40][41].

Because of the high incidence of SMN observed after malignant lymphomas in these seminal studies [39][40][41], many subsequent studies analysed the particular risk of developing a secondary cancer after a special subtype of lymphoid and haematopoietic cancers [1]-[22][42] [43].

3.5.2 Secondary neoplasm after lymphoid and haematopoietic cancer

3.5.2.1 Secondary cancer after Hodgkin lymphoma

Table 2 summarises the major studies on secondary cancers after HL [1]-[9]. The risk of secondary neoplasms after HL has been widely investigated. The actuarial risk of developing a SMN varies between 10% after 20 years [1] and 27% after 25 years of follow-up [9].

Relative risks (RR) of SMN with the exception of non melanomatous skin cancers after HL vary between 2.3 (95% CI 2.2-2.49) [3] and 18.5 (95% CI 15.6-21.7) [1]. The increased RR of acute leukaemia varies between 9.9 [2] and 174.8 [1]. RR of cancers of thyroid, lung, breast and gastrointestinal tract vary between 3.1-36.4, 2.6-27.3, 1.4-56.7 and 1.7-36.4 [1]-[9]. Leukaemias generally appeared during the first five years following HL. Solid cancers occurred mostly later, around 10-15 years after HL. Generally the risk of developing a SMN is higher when HL has been diagnosed at a young age. The risk of SMN increased likewise with the time of follow-up [1]-[9].
The influence of the type of therapy has been controversial. Chemotherapy tended to favour the occurrence of leukaemia. Radiotherapy seemed to influence the appearance of solid cancers like thyroid and breast cancers. Mixed therapy or salvage therapy tended to increase the risk of both solid and non solid SMN [1]-[9].

Studies	Participants	Median follow-up	Actuarial risks for all SMN	RR for all SMN (except nmc)	RR for solid cancers	RR for leukaemias	RR for NHL	RR for breast cancers	RR for lung cancers	RR for thyroid cancers	RR for digestive tract cancers	Therapy
Dores Et al. 2002	2'153 SMN in 32'591	254243 py	21.9% at 25 years (solid SMN)	2.3 (2.2 -2.4)	2.0 (1.9- 2.0)	9.9 (8.7-11.2)	5.5 (4.7-6.4)	2 (1.8-2.3)	2.9 (2.6-3.2)	4.1 (3-5.5)	1.7 (1.5-1.8)	after radiotherapy +/- chemotherapy: increased risk of all solid cancers (especially breast and digestive cancers)
Swerdlow Et al. 2000	322 SMN in 5'519	46990 py	14.7% at 20 years	2.9 (2.6-3.2)	n.i.	14.6 (10.7-19.2)	14 (10.5-18.3)	1.4 (0.9-2.1)	3.4 (2.7-4.2)	7.6 (2.7-16.4)	n.i.	after chemotherapy: increased risk of lung cancer and leukaemia; after radiotherapy: increased risk of lung, thyroid and GI cancers; after combined therapy: increased risk of lung and GI cancers and leukaemia
Van Leeuwen Et al. 2000	137 SMN in 1'253	14.1 years	27.7% at 25 years	7.0 (5.9-8.3)	6.1 (5-7.4)	37.5 (22.2-59.2)	21.5 (12.3-34.9)	5.2 (3.4-7.6)	7.0 (3.7-11.9)	15.2 (4.1-39)*	8.4 (5.5-12.3)	after salvage chemotherapy: increased risk of solid cancer
Foss Abrahamsen Et al. 2002	197 SMN in 1'024	14 years	18.8% at 28 years	3.5 (3.1-4.1)	n.i.	ANLL: 13 (7.1-21.8)	24.2 (16.4-34.3)	3.8 (2.4-5.8)	5.1 (3.3-7.5)	n.i.	colon: 1.9 (0.9-3.7)* rectum: 2.7 (1-5.5)*	after chemotherapy and combined chemotherapy and radiotherapy: increased leukaemia (ANLL); after radiotherapy: increased risk of solid cancer (lung, breast, stomach)
Henry Amar Et al. 1992	631 SMN in 12'411	8.1 years	18.6% at 20 years	n.i.	M: 1.74 W: 1.67	M: 29 W: 26	n.i.	n.i.	n.i.	n.i.	n.i.	after MOPP therapy: increased risk of leukaemia; after extended irradiation +/-chemotherapy: increased risk of solid cancer
Bhatia Et al. 2003	143 SMN in 1'380	11.7 years	10.6% at 20 years	18.5 (15.6-21.7)	18.5 (15.2-22.3)	174.8 (115.1-254.3)	11.7 (4.7-24.2)*	56.7 (40.5-77.3)	27.3 (7.4-69.9)*	36.4 (21.9-56.8)	colorectal: 36.4 (15.7-71.8)*	n.i.
Boivin Et al. 1995	595 SMN in 10'472	7.1 years	n.i.	2.7 (2.5-4.2)	n.i.	23.9 (19.9-36.2)	5.6 (3.9-8.5)	1.4 (1.0-2.1)	respiratory syst and intrathoracic organs: 2.6 (2.1-4.0)	4.5 (2.4-7.7)	1.8 (1.4-2.7)	after chemotherapy: increased risk of cancer of bone, joint, articular cartilage, soft tissues, genital tracts and leukaemia
Hodgson Et al. 2007	1'490 SMN in 18'862	12.2 years	M: 10.5% W: 24.3% at 20 years	2.38 (2.26-2.51)	n.i.	n.i.	n.i.	6.1 (4.7-7.6)	6.7 (5.6-7.8)	3.1 (1.8-5.2)	colon: 4.3 (3.2-5.6)	after radiotherapy and mixed therapy: increased risk of breast and supradiaphragmatic cancers
Metayer Et al. 2000	195 SMN in 5'925	n.i.	n.i.	7.7 (6.6-8.8)	7.0 (5.9-8.2)	20.9 (13.9-30.3)	6.9 (3.3-12.8)	14.1 (p<0.05)	5.1 (1.9-11.1)*	13.7 (8.6-20.7)	colon: 4.7 (1.3-12.1) *	n.i.

* n SMN< 10 nmc: non melanomatous skin cancer py: person-years M: men W: women n.i.: not indicated ANLL: acute non-lymphocytic leukemia MOPP: Mustargen, Oncovin, Procarbazine, Prednisone

Table 2: Main studies on secondary cancers after HL [1]-[9].

3.5.2.2 Secondary cancer after non Hodgkin lymphoma

Unlike HL, there is still little information in the literature on secondary cancers in patients with NHL due to the heterogeneity of tumour histotype and variable treatment.

Cumulative incidence of any SMN after NHL has been 2.5% (95% CI 1.04-3.96) within 30 years from diagnosis of NHL in the study of Maule et al. [15]. Increased standardized incidence ratios (SIR) of secondary cancers in 2'563 NHL survivors have been 40.4 for thyroid cancers (six cases, 95% CI 14.8-88.0) and 6.97 for brain cancer (four cases, 95% CI 1.90-17.9) [15]. A second study [16] analysed the risk of SMN in 2'456 NHL patients and found 123 SMN. RR have been significantly elevated for all secondary cancers (RR 1.3; 95% CI 1.1-1.6), leukaemia (RR 8.8; 95% CI 5.1-14.1) and lung cancer (RR 1.6; 95% CI 1.1-2.3) [16]. Secondary bladder cancers have been reported with an increased incidence in cyclophosphamide treated NHL patients [17].

3.5.2.3 Secondary cancer after hairy cell leukaemia

Findings of the main studies on secondary cancers after hairy cell leukaemias (HCL) have been variable [10][11][12]. Some studies showed that patients with HCL did not have an increased risk of developing a SMN [11][12]. To the contrary, a recent study in 2007 estimated an actual risk of SMN of 31.9% at 25 years of follow up [13].
Increased incidences of secondary gastrointestinal, lung, thyroid and prostate cancers have been observed [13][14]. Generally, risks of lymphoid cancers like HL, NHL and MM after HCL, tended to be increased, but not all data showed a statistical significance [13][14]. Especially high incidences of malignancy occurring before and during HCL, have been observed [13][14].
The development of SMN has been highest in the period up to 2 years after diagnosis of the first tumour [13][14]. The role of the therapy as causative agent in the development of SMN and in particular a study on the role of Interferon has been controversial [13][14].

3.5.2.4 Secondary cancer after other lymphoid and haematopoietic cancers (MALT lymphomas, MCL, CLL, ALL)

In the literature, other studies analysed the risk of secondary malignancies following mantle cell lymphomas (MCL) [42] and MALT lymphomas [43]. There was no clear statistical evidence that solid cancers occurred more frequently after these specific tumours of haematopoietic and lymphoid tissues [42][43]. Some studies found significant increases in the incidence of melanoma and brain and lung cancers among CLL patients [18][19]. The incidence of secondary cancers after diagnosis of childhood ALL remains low [20][22] except for children diagnosed at the age of five or younger and those that received radiation. These children are at higher risk especially for secondary tumours arising in the central nervous system [21] .

3.6 Hypothesis: tumours sharing same etiological factors should be associated

Most of the above mentioned studies [1]-[22][42][43] investigated the incidence of cancers subsequent to the diagnosis of lymphoid and haematopoietic cancers. The inverse, studying the incidence of lymphoid and haematological tumours after a diagnosis of solid cancers has rarely been performed [23]. Therefore we undertook this study to analyse the incidence of cancers which occurred before the diagnosis of lymphoid and haematological tumours.

We analysed the data set on haematopoietic stem cell diseases and lymphoid cancers and their associated cancers from the cancer registry of the Canton of Zurich including data from January 1980 to June 2008. We expected that associated tumours would share similar etiological factors, be they known or hitherto unknown.

4 Materials and methods

4.1 Cancer registry of the Canton of Zurich

4.1.1 Purpose of cancer registry

The cancer registry of the Canton of Zurich was founded in 1980 and collects all data on the incidence of malignant tumours among the residents of this Canton and serves as a basis for epidemiological and clinical research.

4.1.2 Covered population of the Canton of Zurich

The inhabitants of the Canton of Zurich account for approximately one sixth of the Swiss population (17.2% in 2007, respectively 1'307'567 residents) [44][45].

4.2 Data sample

4.2.1 Origin of data sample

Death certificates from the Federal Office for Statistics and histology, cytology or autopsy reports as well as clinical summaries from hospitals, specialists and general medicine physicians, constitute the available sources of the cancer registry [44].

4.2.2 Old cases and cases diagnosed outside the Canton of Zurich

Older cases (older than 1980) and cases diagnosed outside the Canton of Zurich, have been added from clinical files as well as from other Swiss cancer registries [44].

4.2.3 Characteristics of the data

	pat_id	icd_9	s	geb_dt	tod_dt	fall_id	inz_jahr	gmd	dx_klin	dx_morph	topo	morpho	wohn
1	XX	174.3	F	30.05.1925	06.11.1997	AXX	1997	141		10.09.1997	7440	85003	ZH
	XX	201	F	30.05.1925	06.11.1997	BXX	1997	139		10.09.1997	9630	96563	ZH
2	YY	201	F	01.04.1910	22.05.1984	AYY	1971	9					AF
	YY	174.2	F	01.04.1910	22.05.1984	BYY	1981	9		16.10.1981	7450	81413	ZH

ZH: registered in the cancer registry of the Canton of Zurich AF: old case (older than 1980)

Table 3: Characteristics of the data collected from the cancer registry of the Canton of Zurich

Table 3 shows two examples of the characteristics of the data collected from the cancer registry of the Canton of Zurich. Each patient has a unique identification number (pat_id) and each tumour has been separately recorded (fall_id). Gender (s), birth date (geb_dt) and if applicable year of death (tod_dt), have been registered for every patient. Dates of the diagnosis of tumours of haematopoietic and lymphoid tissues and associated tumours have been extracted.

The dates of the morphologic diagnosis of tumours (month and year of dx_morph) were used to calculate the age at diagnosis and to calculate the interval between two or more associated cancers. When these data were missing, dates of the clinical diagnosis (dx_klin) or the incidence year (month of june and inz_jahr) were used. To determine when the associated cancer was

preceding or following the tumour of haematopoietic and lymphoid tissues, the difference of age at their diagnoses was calculated. In the case of simultaneous cancers (example 1 of Table 3) the associated cancer was considered as preceding the tumour of haematopoietic and lymphoid tissues.

4.3 Inclusion criteria and attributions of ICD-O-1 and-3 codes for tumours of haematopoietic and lymphoid tissues

4.3.1 Inclusion criteria

We extracted our data sample from files of the Canton of Zurich cancer registry by searching for ICD-O-1 and-3 codes of tumours of haematopoietic and lymphoid tissues based on the WHO classification.

4.3.2 Attribution of ICD-O-1 and-3 codes for tumours of haematopoietic and lymphoid tissues

Table 4 shows the attribution of ICD-O-1 and-3 codes for tumours of haematopoietic and lymphoid tissues [30]. Tumours were grouped according to their common histological origin: indolent B cell lymphoma, aggressive B cell lymphoma, T cell lymphoma, haematopoietic stem cell disease (HPSCD including ALL, AML, CML and MDS), MM and HL. The ICD-O-1 code was used in the cancer registry of the Canton of Zurich cancer until 2003, it then was replaced by ICD-O-3 code. For analyses ICD-O-1 codes were converted into ICD-O-3 codes [30].

4.3.3 Selection of eight groups of tumours

Eight tumour groups were finally selected for further analyses due to their high incidences: diffuse large B cell lymphoma (DLBL), lymphoplasmacytic lymphoma (LPL), MCL, MM, CLL, HL, HPSCD and FL.

Subtypes	ICD-O-1 codes	ICD-O-3 codes
Multiple myelomas		
Multiple myeloma	97303, 97311, 98303	9732/3, 9731/3, 9733/3
Extramedullary plasmocytoma	97313	9734/3
Indolent B cell lymphomas		
SLL, CLL	96203, 98233, 99701	9670/3,9823/3, 9960/3
Mantle cell lymphoma	96223, 96773	9673/3
Marginal zone lymphoma	97113	9699/3, 9689/3
LPL, Waldenström's disease	96113, 97613	9671/3, 9761/3
Diffuse centroblastic centrocytic lymphoma	96143	9676/3, 9675/3
Follicular lymphoma	96903, 96923, 96973	9698/3 9691/3 9695/3, 9690/3
Hairy cell leukaemia	99403	9940/3
Prolymphocytic lymphoma	98253	9832/3; 9833/3
Aggressive B cell lymphomas		
Diffuse large B cell lymphoma,NHL, lymphosarcoma NOS	96123, 96323, 96403, 95913	9680/3, 9684/3, 9679/3, 9591/3
Burkitt lymphoma, Indeterminate NHL, non Burkitt lymphoma	97503, 96003	9687/3, 9591/3
T cell lymphomas		
T cell lymphoma, T cell leukaemia	97023, 97043, 98273	9709/3, 9717/3, 9719/3, 9702/3, 9827/3, 9834/3
Mycosis fungoides, Sézary syndrome	97003, 97013	9700/3, 9701/3
AILT	97053, 97671	9705/3, 9767/1
Anaplastic large cell lymphoma	97143	9714/3
HS, lymphohistiocytic lymphoma	97203, 97233	9755/3, 9755/3
Hodgkin lymphomas		
MCHL	96523	9652/3
LDHL	96533	9653/3
NLPHL	96513, 96603	9651/3, 9659/3
NSHL	96563, 96633	9665/3, 9663/3
HL NOS	96503	9650/3
HPSCD: ALL, AML, CML, MDS		
LBL, pre B lymphoma, ALL, ALL NOS	96303, 98213, 98003, 98013, 98203	9728/3, 9729/3, 9727/3, 9835/3, 9836/3, 9800/3, 9801/3, 9823/3
AML M3/M4, AML M2/M5, AML NOS	98653, 98663, 98673, 98603, 98623, 98903, 98923, 98403, 98413, 98613, 98643, 98803, 98913, 99103, 98943, 99891	9866/3, 9867/3, 9860/3, 9891/3, 9840/3, 9861/3, 9860/3, 9891/3, 9910/3, 9983/3, 9874/3
CML, MPD NOS	98633, 98423, 98683, 98933, 99203, 99303, 99501, 99601, 99611, 99621	9863/3, 9963/3, 9950/3, 9945/3, 9930/3, 9950/3, 9975/3, 9961/3, 9962/3
MDS NOS	99890	9989/3, 9980/3, 9985/3

Table 4: Attribution of ICD-O-1 and-3 codes for tumours of haematopoietic and lymphoid tissues [30]

4.4 Exclusion criteria

Names of excluded ICD-O-1 codes		ICD-O-1
Malignant lymphoma not other specified (NOS)	Malignant lymphoma NOS	95903
Miscellaneous myeloid diseases	Letterer-Siwe's disease, acute differentiated progressive histiocytosis, acute progressive histiocytosis, acute reticulosis of infancy, acute infantile reticuloendotheliosis, non-lipid reticuloendotheliosis	97223
	Malignant mastocytosis, systemic tissue mast cell disease	97413
	Monoclonal gammopathy	97651
	Leukaemias NOS	98033
	Subacute lymphoid leukaemia, subacute lymphocytic leukaemia, subacute lymphatic leukaemia	98223
	Aleukemic lymphoid leukaemia, aleukemic lymphocytic leukaemia, aleukemic lymphatic leukaemia	98243
	Acute myelofibrosis	99323
	No microscopic confirmation, clinically malignant tumour	99903

Table 5: Excluded ICD-O-1 codes

All benign neoplasms which have not been registered systematically, were excluded. ICD-O-1 codes listed in Table 5 were also excluded because of their rarity and lack of specificity. Furthermore 31 patients of a total of 12'829 were eliminated because of unknown dates of the diagnosis of lymphohaematopoietic cancer.

4.5 Associated malignant neoplasms: the definition, ICD-9 and-10 codes and incidence rates

4.5.1 Definition of associated malignant neoplasms

All diagnoses in addition to a tumour of haematopoietic and lymphoid tissues that occurred during a patient's lifetime were registered as associated malignant neoplasms (AMN).

4.5.2 Attribution of ICD-10 codes for associated malignancies

ICD-9 and-10 codes were used to describe the associated cancer. ICD-9 code was used in the cancer registry of the Canton of Zurich until 2003, it then was replaced by ICD-10 code. ICD-9 codes were converted into ICD-10 codes (conversion's table [46]).

ICD-10 codes	Names	ICD-10 codes	Names
C00-C14, C30-C32, C46, C76	Cancer of head and neck	C56	Cancer of ovary
C15	Cancer of esophagus	C51, C52, C57, C58	Cancer of other female genital organs
C16	Cancer of stomach	C61	Cancer of prostate
C18	Cancer of colon	C62	Cancer of testis
C19-21	Cancer of rectum and anus	C60, C63	Cancer of other male genital organs
C22	Cancer of liver and intrahepatic bile duct	C67	Cancer of bladder
C25	Cancer of pancreas	C64, C65	Cancer of kidney and renal pelvis
C17, C23, C24, C26, C45, C48	Cancer of other gastrointestinal organs and peritoneum	C66, C68	Cancer of other urinary organs
C34	Cancer of bronchus and lung	C47, C70-C72	Cancer of brain and nervous system
C33, C38, C39, C45	Other respiratory and intrathoracic cancer	C81	Hodgkin lymphoma
C40, C41, C46, C47, C49	Cancer of bone and connective tissue	C46, C82-85, C96	Non-Hodgkin lymphoma
C43	Melanoma of skin	C90-95	Leukaemia
C44, C46	Other non-epithelial cancer of skin	C88-C90	Multiple myeloma
C50	Cancer of breast	C37, C38, C45, C46, C69, C74-C76, C96	Other and unspecified primary cancer
C54, C55	Cancer of uterus	C77-C79	Secondary malignancy
C53	Cancer of cervix	C80, C97	Malignant neoplasm without specification of site

Table 6: Attribution of ICD-10 for codes for associated malignancies

Table 6 shows the ICD-10 codes used in our study. AMN were categorised in two main groups: non solid and solid tumours.

4.5.3 Incidence rates of associated malignant neoplasms

4.5.3.1 Incidence rates representing the ratio of numbers of AMN to numbers of tumours in selected tumour groups

4.5.3.1.1 Method

To assess the incidence of associated neoplasms among the eight most frequent groups of tumours (DLBL, CLL, HL, LPL, MCL, MM, FL and HPSCD), we calculated the incidence rates as the ratio of numbers of AMN and numbers of cancers of haematopoietic and lymphoid tissues in each group.

$$\text{Incidence rate of AMN} = \frac{n(\text{AMN})_{(\text{DLBL or CLL or HL or LPL or MCL or MM or FL or HPSCD})}}{N_{(\text{DLBL or CLL or HL or LPL or MCL or MM or FL or HPSCD})}}$$

4.5.3.1.2 Numbers of solid AMN

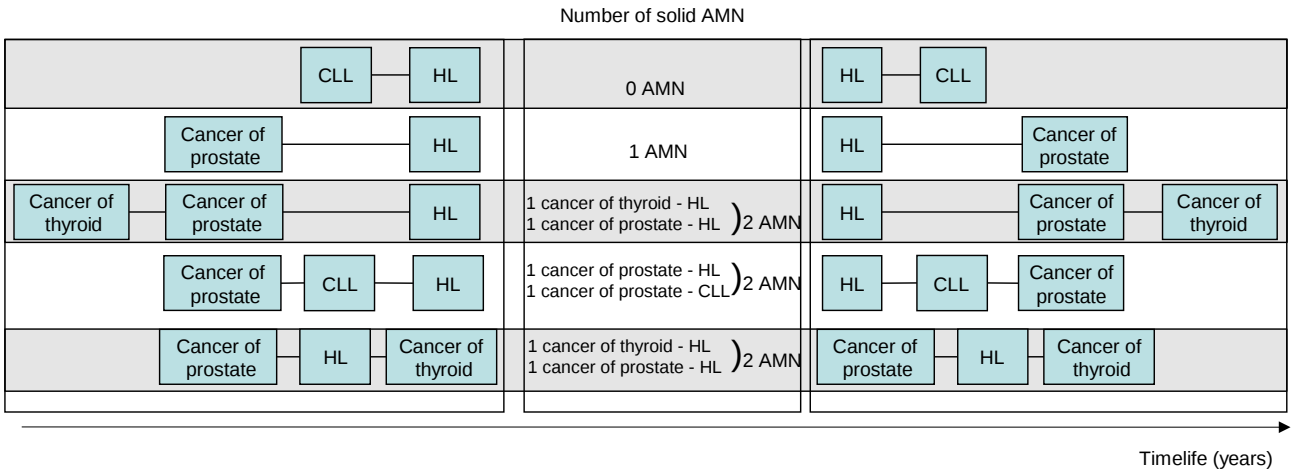


Figure 2: Numbers of solid AMN in different encountered situations: AMN before the diagnosis of the tumour of haematopoietic and lymphoid tissues (on the left side) and AMN after the diagnosis of the tumour of haematopoietic and lymphoid tissues (on the right side)

To simplify the calculation of the incidence rates of AMN and to avoid including cases of lymphoma progression and recurrence, we focused our analyses on solid AMN. Figure 2 shows different variations of associated cancers with their attributed numbers of solid AMN according to cancer associations.

4.5.3.1.3 Age-, date- and gender-specific incidence rates

Incidence rates were analysed for all types of associated malignant neoplasms and grouped into age categories according to the age at diagnosis (5 year age groups) as well as calendar periods of haematopoietic and lymphoid neoplasm registration (<1988, 1989-1997 and >1998). All incidence rate curves were calculated for both genders (M and F) and separately (M or F). Incidence rate curves were obtained with rolling averages over two 5 year age groups.

4.5.3.1.4 Incidence rates among three groups of solid AMN

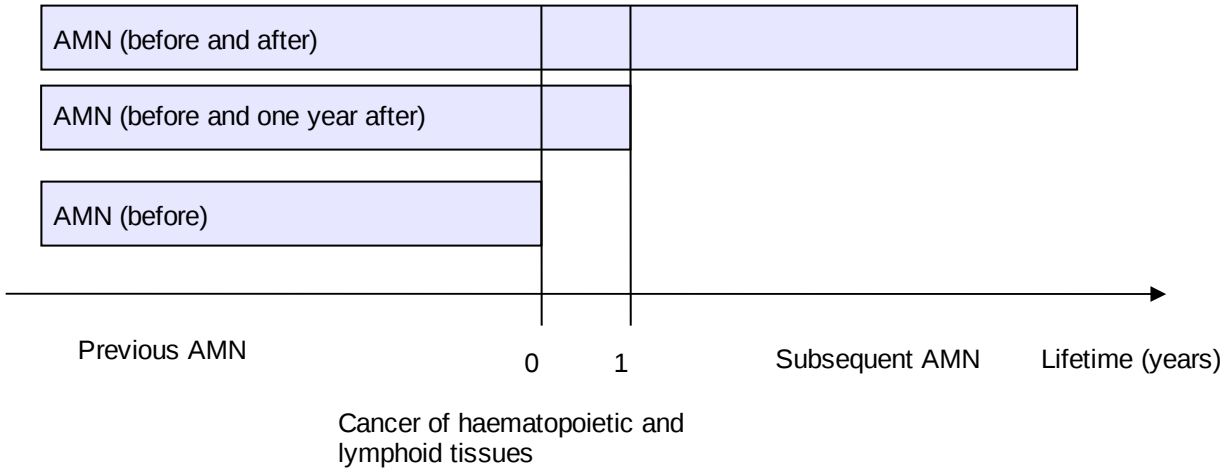


Figure 3: Three groups of AMN: AMN before and after haematopoietic and lymphoid neoplasm (top), previous AMN and AMN in the interval of one year after the lymphohaematopoietic cancer diagnosis (middle) and AMN before the lymphohaematopoietic cancer diagnosis (bottom)

Initially incidence rates were calculated for all solid AMN before and after haematopoietic and lymphoid neoplasm. To reduce the influence of the survival rate of the tumour of haematopoietic and lymphoid tissues on the occurrence of a second associated cancer, we selected two other groups of solid AMN illustrated in Figure 3:

- AMN which occurred only before the lymphohaematopoietic cancer diagnosis
- AMN which occurred before the lymphohaematopoietic cancer diagnosis and in the interval of one year afterwards.

4.5.3.2 Statistical analyses for expected number of associated cancers using a generalized additive model for Poisson regression

4.5.3.2.1 Method

For statistical purposes a generalized additive model (GAM) for Poisson regression has been used in cooperation with Dr. Kaspar Rufibach from the Biostatistics Unit of the Institute of Social and Preventive Medecine of the University of Zurich. AMN rates were calculated as events per time unit of age group of diagnosis of lymphohaematopoietic cancer. Patients were censored at the date of death. When this data was missing patients were censored at the date where the last incidence year of cancer was recorded.
Computations were performed using R, where GAM's were generated via the R-package mgcv [47].

4.5.3.2.2 Excluded AMN in calculation of the expected number of AMN

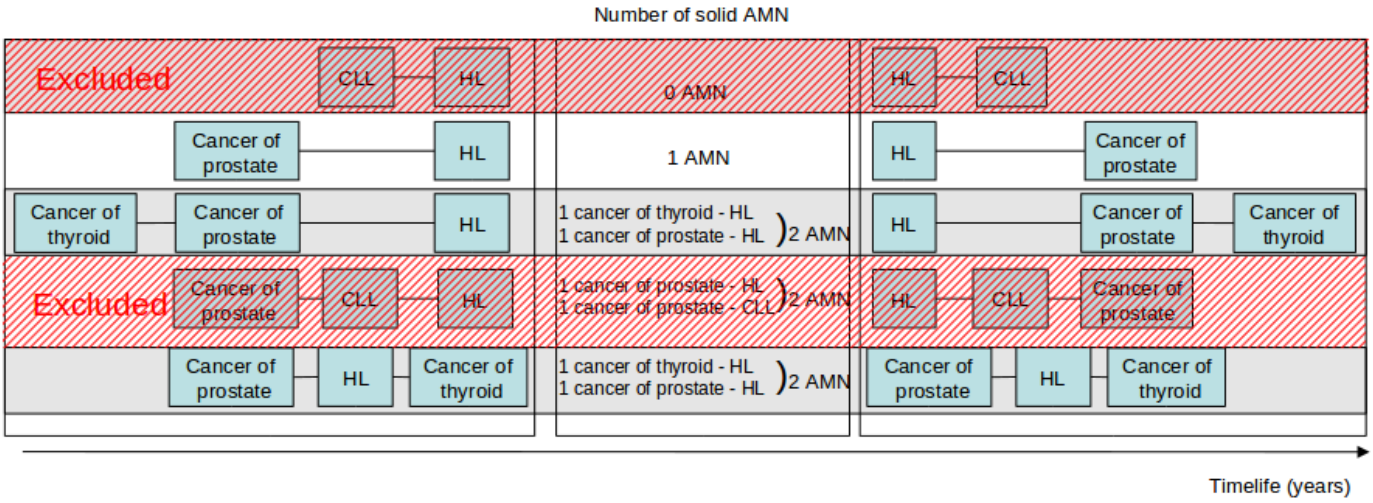


Figure 4: Excluded patients with more than one cancer of haematopoietic and lymphoid tissues: patients with AMN before tumour of haematopoietic and lymphoid tissues (left) and AMN after tumour of haematopoietic and lymphoid tissues (right)

Figure 4 shows different encountered situations of associated cancers. To calculate the estimated number of AMN and to avoid also including cases of lymphoma progression and recurrence, patients with more than one cancer of haematopoietic and lymphoid tissues were excluded.

4.5.3.2.3 Age-and gender-specific expected numbers of AMN

Age-and gender-specific estimated numbers of AMN were calculated for seven groups of tumours (DLBL, CLL, HL, LPL, FL, MM and HPSCD). Gender and group of tumours were entered as nominal variables and the age as a continuous variable. Age was grouped into five year intervals starting at 0. Expected numbers of AMN were studied in the two groups of AMN: all AMN before and after haematopoietic and lymphoid neoplasm and AMN before lymphohaematopoietic cancer.

5 Results

5.1 Numbers of patients, tumours of haematopoietic and lymphoid tissues and AMN

5.1.1 Numbers of patients and tumours of haematopoietic and lymphoid tissues

A total of 12'798 patients with one or more than one cancer of haematopoietic and lymphoid tissues were identified. After excluding all patients with more than one tumour of haematopoietic and lymphoid tissues, 10'923 patients were identified.
Some patients had multiple tumours of haematopoietic and lymphoid tissues, therefore the total number of tumours of haematopoietic and lymphoid tissues was higher and added up to 12'994 tumours.

5.1.2 Numbers of associated malignant neoplasms

Table 8 shows the number of every type of solid and non solid AMN among the main groups of tumours of haematopoietic and lymphoid tissues. In total we detected 2'885 previous and subsequent AMN in 12'798 patients (439 non solid AMN and 2'446 solid AMN). The most frequent solid AMN are cancers of prostate (433 cases), cancers of breast (354 cases), cancers of lung (227 cases), cancers of colorectum (295 cases). After excluding patients with more than one cancer of haematopoietic and lymphoid tissues, we detected 2'374 previous and subsequent AMN in 10'923 patients.

5.1.3 Number of AMN per patient

Among 12'798 patients with one or more than one cancer of haematopoietic and lymphoid tissues, 2'061 patients had one associated malignant neoplasm and 313 patients had more than one AMN.

Number of AMN per patient		Numbers of patients			sex ratio
		total	men	women	men/women
0		**10424**	**5513**	**4911**	**1.12**
1		**2061**	**1183**	**878**	**1.35**
>1		**313**	**193**	**120**	**1.61**
	2	273	168	105	1.6
	3	34	23	11	2.09
	4	5	2	3	0.67
	5	1	0	1	0

Table 7: Numbers of AMN per patient, numbers of patients and sex ratios

Table 7 shows the number of patients with 0, 1 and more than 1 AMN and their sex ratios. There was a male predominance in most of the groups of patients with one or more than one AMN.

Numbers of AMN	HL	HPSCD	Aggressive B cell lymphomas	MM	Indolent B cell lymphomas	T cell lymphomas	Total
Tumours of haematopoietic and lymphoid tissues	**1011**	**3125**	**2107**	**1902**	**4108**	**505**	**12758**
AMN	**266**	**652**	**417**	**347**	**1076**	**127**	**2885**
Non solid AMN	**57**	**171**	**55**	**37**	**98**	**21**	**439**
Leukemias	15	95	20	18	42	11	201
Non-Hodgkin lymphoma	37	47	7	16	26	5	138
Multiple myeloma	4	18	8	2	16	3	51
Hodgkin lymphoma	1	11	20	1	14	2	49
Solid AMN	**209**	**481**	**362**	**310**	**978**	**106**	**2446**
Cancer of bladder	10	37	23	28	58	7	163
Cancer of bone and connective tissue	4	4	7	2	12	5	34
Cancer of brain and nervous system	0	2	1	1	13	1	18
Cancer of breast	45	47	45	48	158	11	354
Cancer of bronchus, lung	42	32	28	23	90	12	227
Cancer of cervix	1	9	5	2	12	2	31
Cancer of colon	12	48	21	28	71	4	184
Cancer of esophagus	6	5	2	4	3	0	20
Cancer of head and neck	12	11	14	5	37	3	82
Cancer of kidney and renal pelvis	0	0	0	0	0	0	0
Cancer of liver and intrahepatic bile duct	5	3	7	3	8	2	28
Cancer of other female genital organs	4	12	5	9	21	2	53
Cancer of other GI organs, peritoneum	1	5	2	4	19	0	31
Cancer of other male genital organs	0	1	1	1	0	3	6
Cancer of other urinary organs	6	17	13	9	22	1	68
Cancer of ovary	0	0	0	0	0	0	0
Cancer of pancreas	6	7	5	5	17	1	41
Cancer of prostate	14	102	69	61	164	23	433
Cancer of rectum and anus	6	31	15	17	40	2	111
Cancer of stomach	3	13	14	8	39	0	77
Cancer of testis	0	10	3	2	3	2	20
Cancer of thyroid	5	11	7	7	17	2	49
Cancer of uterus	2	20	12	15	36	1	86
Melanoma of skin	12	29	26	13	64	7	151
Other non-epithelial cancer of skin	8	18	36	12	66	15	155
Malignant neoplasm without specification of site and other respiratory and intrathoracic cancer	14	12	4	6	24	0	60

Table 8: Numbers of AMN in patients with one or more than one tumour of haematopoietic and lymphoid tissues

5.2 Characteristics of patients with AMN: a comparison of two populations

5.2.1 Average age and sex ratio of patients with AMN

5.2.1.1 Average age

As a reference group we chose to compare the characteristics of patients with AMN with characteristics of all patients with one or more tumours of haematopoietic and lymphoid tissues.

Average age at diagnosis of haematopoietic and lymphoid cancer among patients with AMN is 68 years. In comparison the average age at diagnosis of all patients with tumours of haematopoietic and lymphoid tissues is 63.

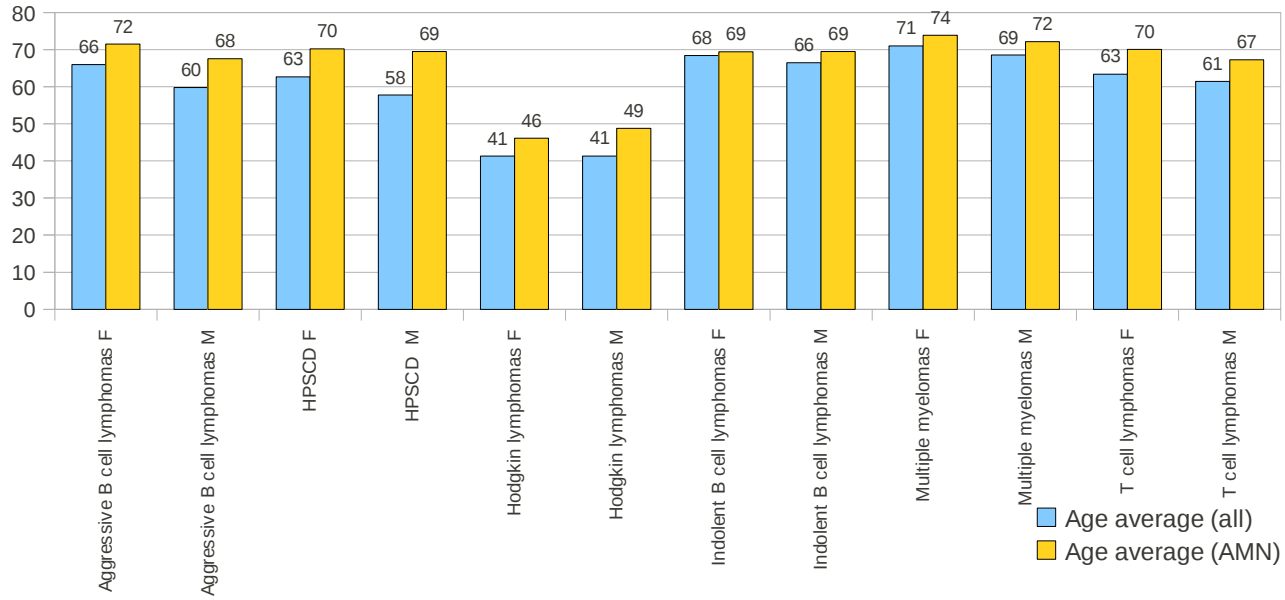


Figure 5: Average age of groups of tumours of haematopoietic and lymphoid tissues among men and women in the two populations: patients with tumours of haematopoietic and lymphoid tissues and patients with AMN

Figure 5 shows the average age at time of diagnosis of the main groups of tumours of haematopoietic and lymphoid tissues among women and men.

Among women, the average age at diagnosis of haematopoietic and lymphoid cancer is slightly higher in the two groups of populations.

5.2.1.2 Sex ratio

Sex ratios show a male predominance with an average of 1.3 in the group of AMN and of 1.2 in all patients.

5.2.2 Numbers of AMN per thousand tumours of haematopoietic and lymphoid tissues in patients with AMN

Table 9 describes the numbers of AMN per thousand lymphohaematopoietic tumours, sex ratios and age averages for every group of cancer in all patients with one or more tumours of haematopoietic and lymphoid tissues (first column) and in patients with AMN (second column). Patients with AMN include patients with solid and non solid AMN as well as previous and subsequent AMN.

An average of 205 in 1'000 lymphohaematopoetic cancers are associated with another cancer. AMN are most frequently associated with indolent B cell lymphomas as well as Hodgkin lymphomas (237cases/1'000 for both).

Characteristics	All patients with tumours of haematopoietic and lymphoid tissues					Patients with associated malignant neoplasms					
	Numbers of AMN			Sex ratios	Age averages	Numbers of AMN			Sex ratios	Age averages	Per thousand
	M and F	F	M			M and F	F	M			
All tumours of haematopoietic and lymphoid tissues	12994	5997	6997	1.2	63	2662	1142	1520	1.3	68	205
Multiple myelomas	1933	924	1009	1.1	69.7	333	159	174	1.1	72.9	172
Multiple myeloma	1896	909	987	1.1	69.8	321	155	166	1.1	73	169
Extramedullary plasmocytoma	37	15	22	1.5	65.6	12	4	8	2	70.8	324
Indolent B cell lymphomas	4190	1964	2226	1.1	67.4	991	434	557	1.3	69.4	237
SLL, CLL	2091	933	1158	1.2	70.1	545	221	324	1.5	71.4	261
Mantle cell lymphoma	267	92	175	1.9	67.4	55	16	39	2.4	69.1	206
Marginal zone lymphoma	293	173	120	0.7	64.6	76	46	30	0.7	70.2	259
LPL Waldenstrom disease	482	224	258	1.2	68.8	119	59	60	1	68.5	247
Diffuse centroblastic centrocytic lymphoma	321	178	143	0.8	65.4	66	35	31	0.9	65.1	206
Follicular lymphoma	566	321	245	0.8	61	93	47	46	1	63.7	164
Hairy cell leukaemia	154	37	117	3.2	58.6	33	8	25	3.1	63.9	214
Prolymphocytic lymphoma	16	6	10	1.7	68.6	4	2	2	1	67.8	250
Aggressive B cell lymphomas	2147	997	1150	1.2	62.6	383	159	224	1.4	69.2	178
Diffuse large B cell lymphoma, NHL, lymphosarcoma NOS	2018	954	1064	1.1	63.6	369	154	215	1.4	69.6	183
Burkitt lymphoma, Indeterminate NHL , non Burkitt NHL	129	43	86	2	47	14	5	9	1.8	57.7	109
T cell lymphomas	515	220	295	1.3	62.3	112	37	75	2	68.2	217
T cell lymphoma, T cell leukamia	202	98	104	1.1	62.1	33	13	20	1.5	66.7	163
Mycosis fungoides, Sezary syndrome	134	50	84	1.7	65.4	36	8	28	3.5	67.8	269
AILT	48	25	23	0.9	68.4	13	7	6	0.9	76.7	271
Anaplastic large cell lymphoma	110	40	70	1.8	57.2	22	6	16	2.7	65	200
HS, lymphohistiocytic lymphoma	21	7	14	2	56.4	8	3	5	1.7	70.4	381
Hodgkin lymphomas	1015	441	574	1.3	41.3	241	110	131	1.2	47.5	237
MCHL	198	74	124	1.7	45.8	37	17	20	1.2	57	187
LDHL	33	10	23	2.3	59.6	10	2	8	4	70.9	303
NLPHL	78	21	57	2.7	41.8	19	4	15	3.8	54.6	244
NSHL	526	250	276	1.1	37.9	63	30	33	1.1	51.6	120
HL NOS	180	86	94	1.1	42.9	112	57	55	1	38.9	622
HPSCD (ALL, AML, CML, MDS)	3194	1451	1743	1.2	60	602	243	359	1.5	69.8	188
LBL, Pre B cell lymphoma, ALL, Acute lymphatic leukaemia NOS	494	212	282	1.3	33.7	40	18	22	1.2	63.4	81
AML M3/M4, AML M2/M5, AML NOS	1344	624	720	1.2	64.2	257	113	144	1.3	70	191
CML MPD NOS	850	399	451	1.1	64.1	171	64	107	1.7	68.1	201
MDS NOS	506	216	290	1.3	67.6	134	48	86	1.8	73.3	265

Table 9: *Numbers of AMN per thousand tumours of haematopoietic and lymphoid tissues in all patients with one or more than one tumour of haematopoietic and lymphoid tissues and patients with AMN*

5.3 Illustrations of lymphohaematopoietic cancers and their associated malignancies with scatter diagrams

5.3.1 Lymphohaematopoietic cancers and their associated solid malignancies

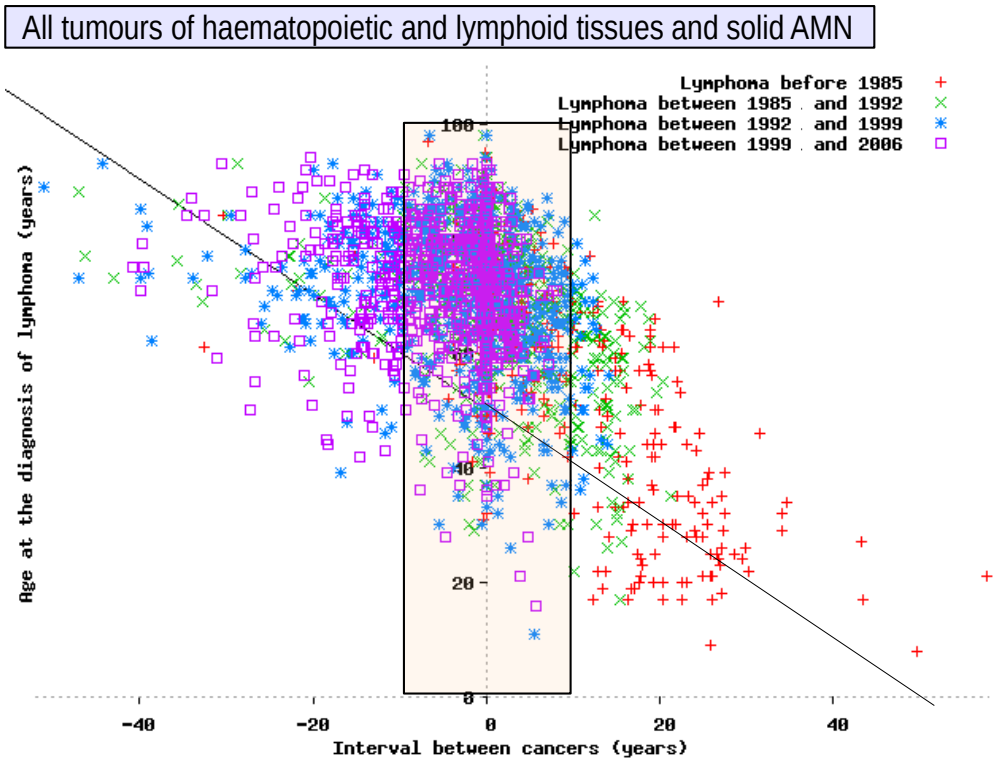


Figure 6: Scatter diagram: all lymphohaematopoietic cancers and their associated solid malignancies

Figure 6 shows the scatter diagram of lymphohaematopoietic cancers and their associated solid malignancies. The x-axis shows the time interval in years between the tumour of haematopoietic and lymphoid tissues and the associated cancer. The y-axis shows the age at diagnosis of lymphohaematopoietic cancer in years. Furthermore calendar years at diagnosis of the lymphohaematopoietic cancer are indicated with different symbols (in the legend). The orange rectangle defines the interval of 10 years before and after lymphohaematopoietic cancers. Cases of AMN which have been diagnosed before or at the age of 50 are represented below the diagonal black line.

The scatter diagram describes a trapezoid figure. Diagnoses of lymphohaematopoietic cancers in young people (most of all in the 1980's) are followed by subsequent AMN (right part of the scatter diagram). In contrast a predominance of previous AMN was observed among the oldest population (left part of the scatter diagram). Most of AMN occur within the interval of 10 years before and after lymphohaematopoietic cancers diagnosed between 50 and 90 years.

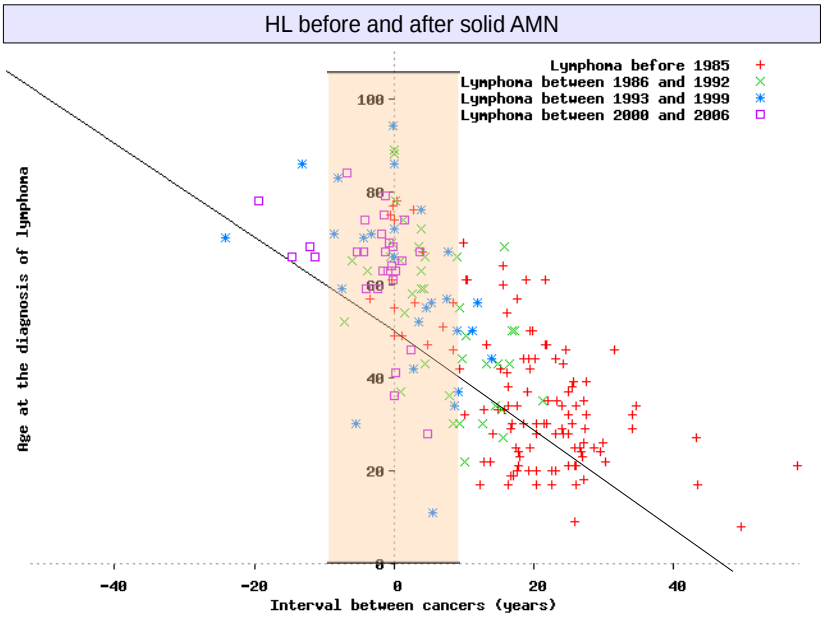
5.3.2 DLBL, CLL, HL, LPL, MCL, MM, HPSCD, FL and their associated solid malignancies

Figure 7 to 14 show scatter diagrams of a subtype of lymphohaematopoietic cancers and their associated malignancies. The x-axis shows the time interval between the subtype of tumour of haematopoietic and lymphoid tissues and the associated solid cancer in years. The y-axis shows the age at diagnosis of the subtype of lymphohaematopoietic cancer in years. Furthermore calendar years at diagnosis of the lymphohaematopoietic cancer are indicated with different symbols (in the legend). The orange rectangle defines the interval of 10 years before and after the subtype of lymphohaematopoietic cancers. Cases of AMN which have been diagnosed before or at the age of 50 are represented below the diagonal black line. The right side of the figure 7 to 14 shows the exact numbers of lymphohaematopoietic cancers , numbers of solid AMN and incidence rates of solid AMN.

Figure 7 to 14 show that most of the solid AMN occur within the interval of 10 years before and after DLBL, FL, MCL, LPL and CLL. AMN occur mainly after HL was diagnosed in childhood. AMN appear mainly before HPSCD diagnosed in an older population.

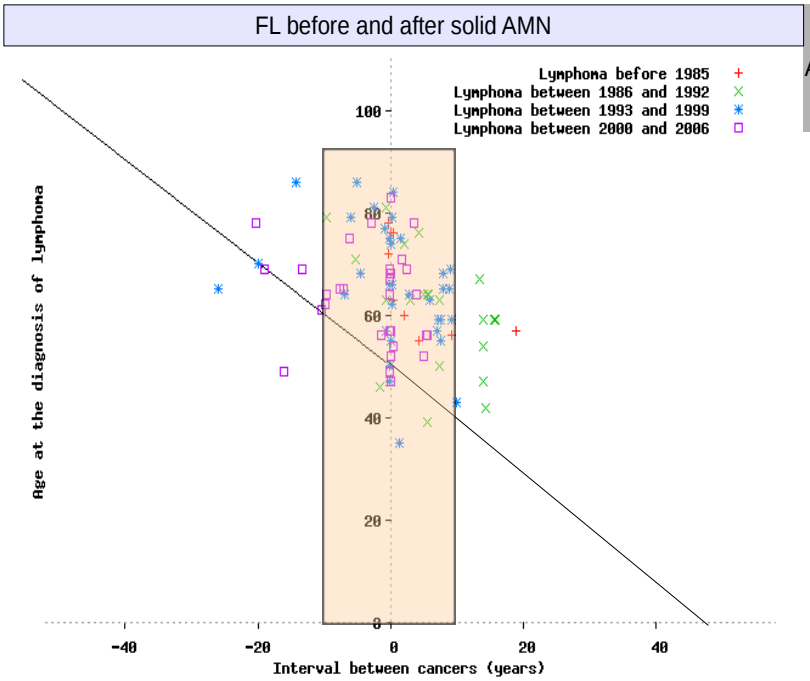
HL and HPSCD have the highest rate of associated malignancies before the age of 50 (cases represented below the black line).

The scatter diagram of HL illustrates less AMN in comparison with the scatter diagrams of MM, DLBL, CLL and HPSCD. But the exact data in the tables shows an higher incidence rate of solid AMN in HL patients.



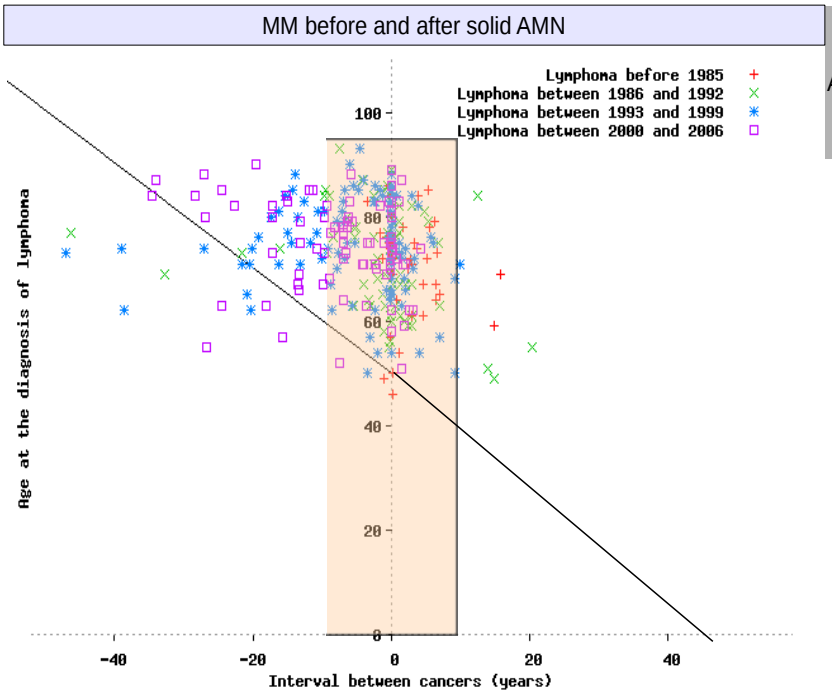
Age range	Number of lymphohaematopoietic cancers	Number of solid AMN	Incidence rate of solid AMN
0-4	1	0	0
5-9	9	2	0.22
10-14	30	1	0.03
15-19	67	9	0.13
20-24	125	19	0.15
25-29	107	19	0.18
30-34	120	25	0.21
35-39	90	14	0.16
40-44	99	17	0.17
45-49	47	12	0.26
50-54	55	11	0.2
55-59	50	16	0.32
60-64	42	14	0.33
65-69	58	22	0.38
70-74	37	12	0.32
75-79	39	9	0.23
80-84	20	2	0.1

Figure 7: Scatter diagram: HL and their associated solid malignancies



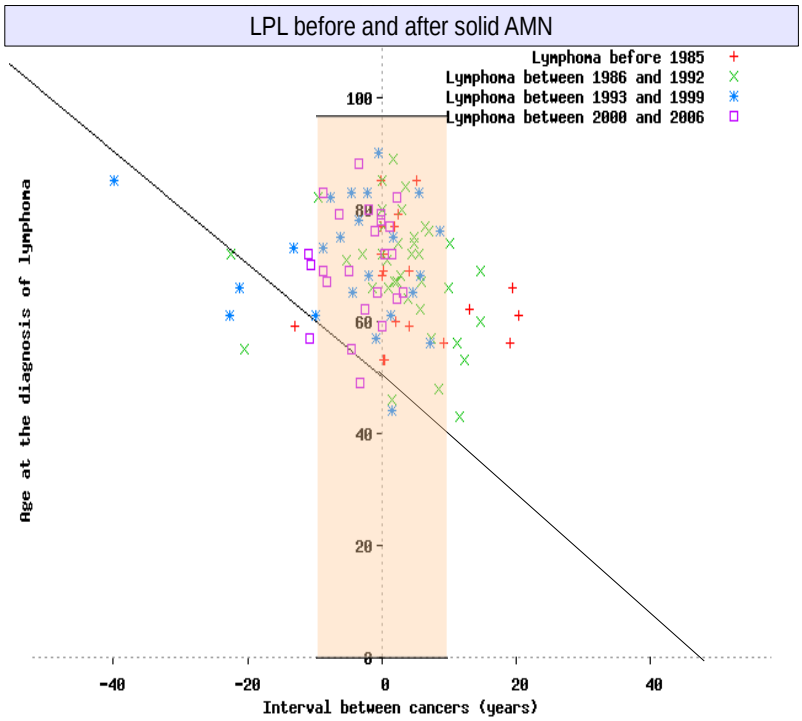
Age range	Number of lymphohaematopoietic cancers	Number of solid AMN	Incidence rate of solid AMN
0-4	0	0	/
5-9	0	0	/
10-14	0	0	/
15-19	1	0	0
20-24	2	0	0
25-29	3	0	0
30-34	8	0	0
35-39	22	2	0.09
40-44	31	2	0.06
45-49	44	6	0.14
50-54	78	6	0.08
55-59	77	19	0.25
60-64	67	17	0.25
65-69	70	19	0.27
70-74	57	6	0.11
75-79	49	14	0.29
80-84	35	4	0.11

Figure 8: Scatter diagram: FL and their associated solid malignancies



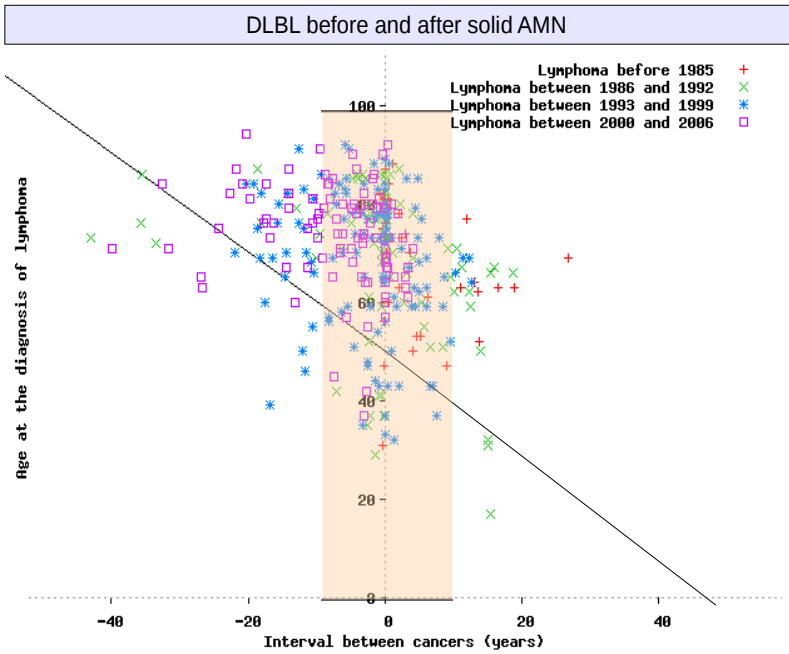
Age range	Number of lymphohaematopoietic cancers	Number of solid AMN	Incidence rate of solid AMN
0-4	0	0	/
5-9	0	0	/
10-14	0	0	/
15-19	1	0	0
20-24	0	0	/
25-29	1	0	0
30-34	2	0	0
35-39	17	0	0
40-44	45	1	0.02
45-49	64	4	0.06
50-54	91	10	0.11
55-59	163	14	0.09
60-64	194	30	0.15
65-69	278	35	0.13
70-74	326	73	0.22
75-79	320	60	0.19
80-84	266	52	0.20

Figure 9: Scatter diagram: MM and their associated solid malignancies



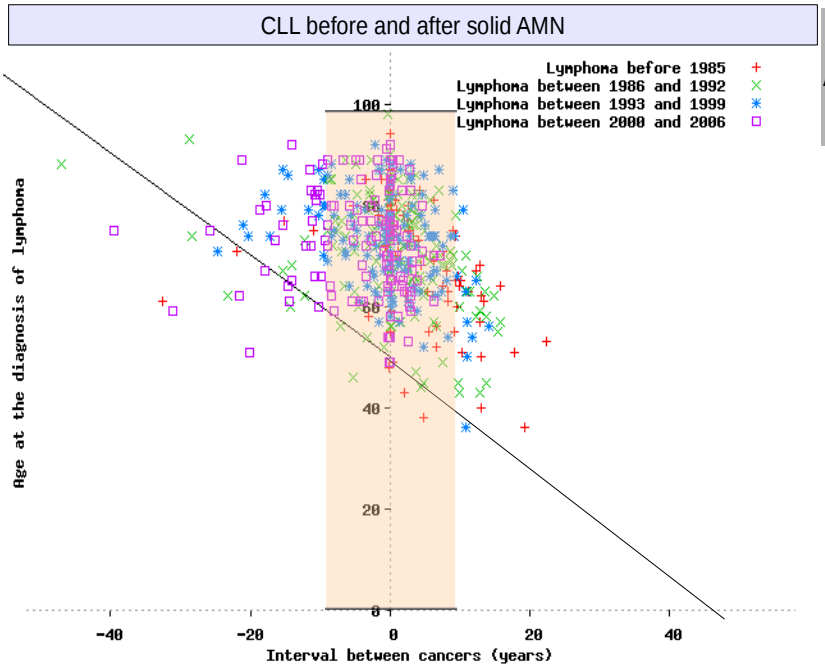
Age range	Number of lymphohaematopoietic cancers	Number of solid AMN	Incidence rate of solid AMN
0-4	0	0	/
5-9	0	0	/
10-14	1	0	0
15-19	0	0	/
20-24	0	0	/
25-29	2	0	0
30-34	3	0	0
35-39	3	0	0
40-44	11	2	0.18
45-49	18	3	0.17
50-54	31	3	0.10
55-59	51	12	0.24
60-64	39	11	0.28
65-69	66	25	0.38
70-74	75	18	0.24
75-79	71	17	0.24
80-84	69	11	0.16

Figure 10: Scatter diagram: LPL and their associated solid malignancies



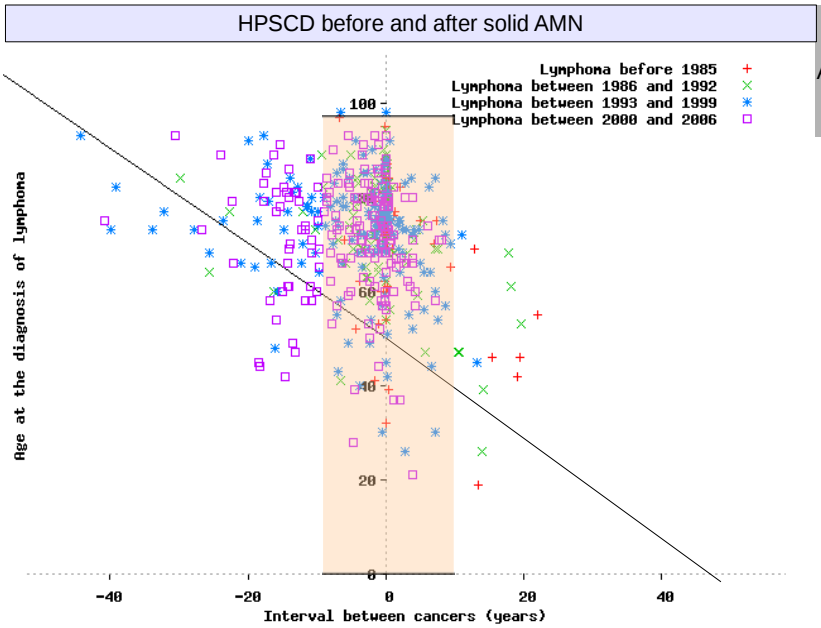
Age range	Number of lymphohaematopoietic cancers	Number of solid AMN	Incidence rate of solid AMN
0-4	2	0	0
5-9	12	0	0
10-14	4	0	0
15-19	23	1	0.04
20-24	24	0	0
25-29	48	1	0.02
30-34	67	5	0.07
35-39	78	8	0.10
40-44	78	11	0.14
45-49	94	6	0.06
50-54	120	14	0.12
55-59	161	20	0.12
60-64	178	30	0.17
65-69	184	46	0.25
70-74	256	53	0.21
75-79	276	67	0.24
80-84	242	54	0.22

Figure 11: Scatter diagram: DLBL and their associated solid malignancies



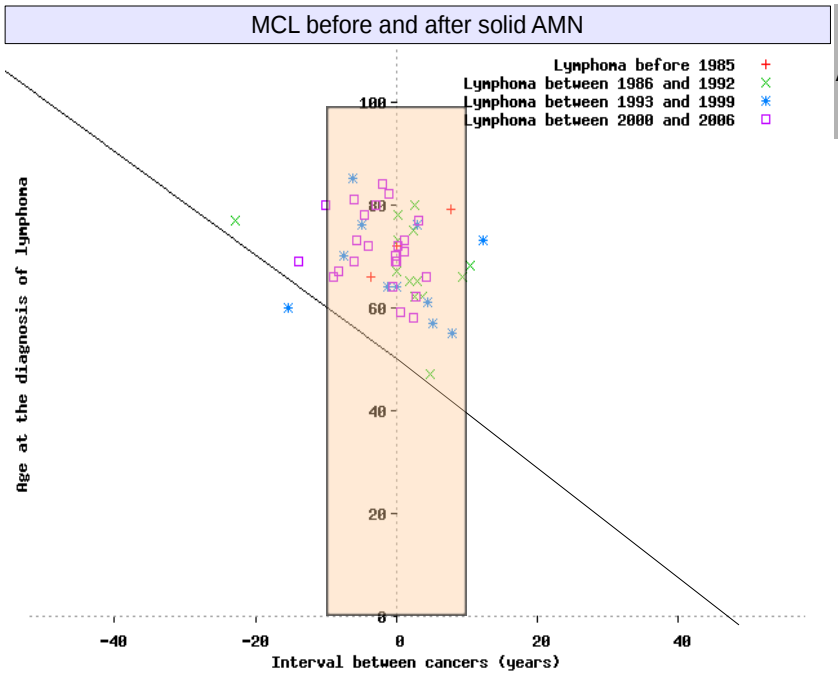
Age range	Number of lymphohaematopoietic cancers	Number of solid AMN	Incidence rate of solid AMN
0-4	0	0	/
5-9	0	0	/
10-14	0	0	/
15-19	3	0	0
20-24	2	0	0
25-29	6	0	0
30-34	5	0	0
35-39	23	3	0.13
40-44	31	5	0.16
45-49	53	10	0.19
50-54	108	17	0.16
55-59	168	32	0.19
60-64	242	77	0.32
65-69	271	75	0.28
70-74	325	101	0.31
75-79	354	102	0.29
80-84	264	64	0.24

Figure 12: Scatter diagram: CLL and their associated solid malignancies



Age range	Number of lymphohaematopoietic cancers	Number of solid AMN	Incidence rate of solid AMN
0-4	134	0	0
5-9	74	0	0
10-14	49	0	0
15-19	35	1	0.03
20-24	59	1	0.02
25-29	71	3	0.04
30-34	62	3	0.05
35-39	89	5	0.06
40-44	109	11	0.10
45-49	114	14	0.12
50-54	144	14	0.10
55-59	184	27	0.15
60-64	239	36	0.15
65-69	314	64	0.20
70-74	430	94	0.22
75-79	463	88	0.19
80-84	354	79	0.22

Figure 13: Scatter diagram: HPSCD and their associated solid malignancies



Age range	Number of lymphohaematopoietic cancers	Number of solid AMN	Incidence rate of solid AMN
0-4	0	0	/
5-9	0	0	/
10-14	0	0	/
15-19	0	0	/
20-24	0	0	/
25-29	1	0	0
30-34	3	0	0
35-39	5	0	0
40-44	6	0	0
45-49	6	1	0.17
50-54	16	0	0
55-59	24	4	0.17
60-64	35	8	0.23
65-69	52	13	0.25
70-74	34	10	0.29
75-79	39	8	0.21
80-84	34	7	0.21

Figure 14: Scatter diagram: MCL and their associated solid malignancies

5.4 Incidence rates of associated malignant neoplasms

5.4.1 Incidence rates representing the ratio of numbers of AMN to numbers of tumours in selected groups of tumours

5.4.1.1 Age-and gender-specific incidence rates of associated solid malignancies before and after tumour of haematopoietic and lymphoid tissues

Figure 15 shows the incidence rate curves of associated solid malignancies before and after a subtype of tumour of haematopoietic and lymphoid tissues (MM, DLBL, HL, LPL, CLL, HPSCD, FL and MCL) among men and women and each one separately. The x-axis shows the age at diagnosis of lymphohaematopoietic cancer in 5 year intervall age groups (in years). The y-axis shows the incidence rate of solid AMN in each age group.

There is a gradual increase of the incidence rate of solid AMN in each tumoral group with age at diagnosis. The highest incidence rate of AMN occurs among HL patients with a peak-incidence at 65-74 year old.

A steeper increase in the incidence rate with age is observed among men while the increase is more gradual among women.

5.4.1.2 Age-and gender-specific incidence rates of associated solid malignancies before tumour of haematopoietic and lymphoid tissues

Figure 16 shows the incidence rate curves of associated solid malignancies before tumour of haematopoietic and lymphoid tissues among men and women and each one separately.

The gradual increase in age at diagnosis is still observed in these incidence rate curves.

Contrary to other groups of tumours a peak-incidence rate of solid AMN among HL persists at 70-74 year old (particularly among women). Among other groups of tumours of haematopoietic and lymphoid tissues only few differences of incidence rates are observed.

5.4.1.3 Age-and gender-specific incidence rates of associated solid malignancies before and 1 year after tumour of haematopoietic and lymphoid tissues

Figure 17 shows the incidence rate curves of associated solid malignancies before and one year after tumour of haematopoietic and lymphoid tissues among men and women and each one separately. Few differences are observed between Figure 16 and Figure 17.

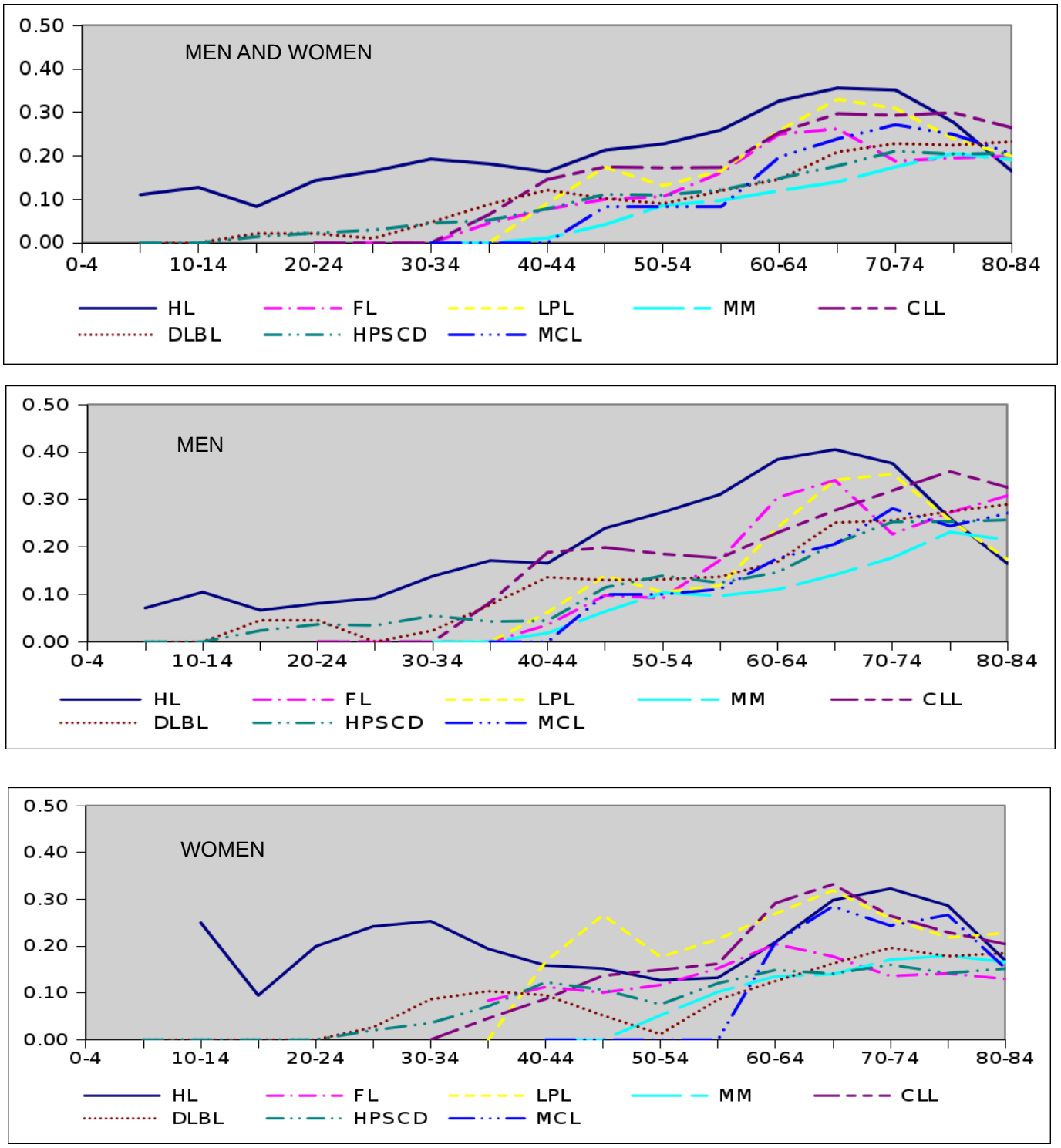
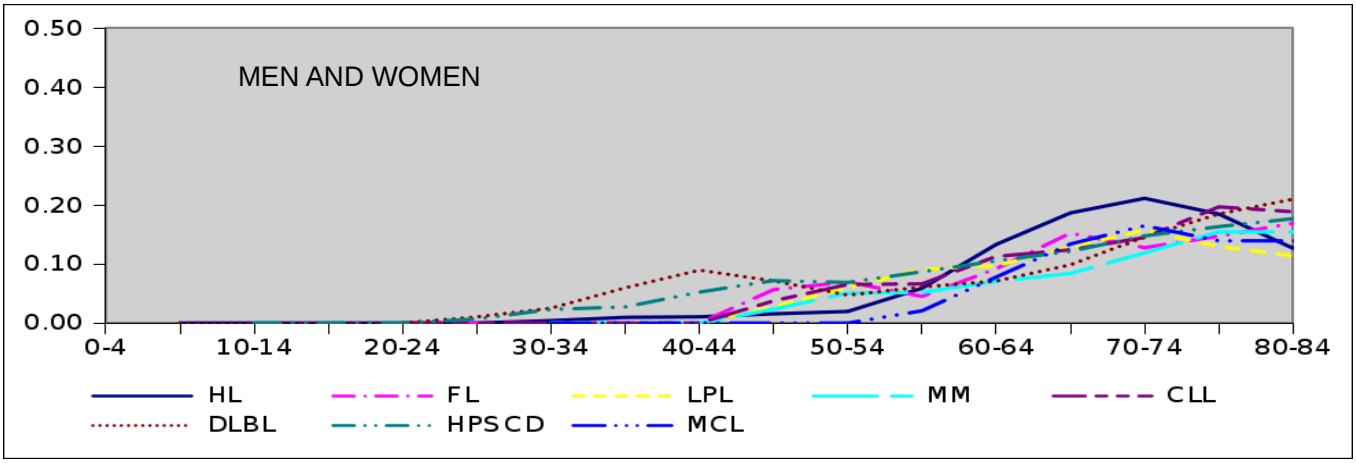
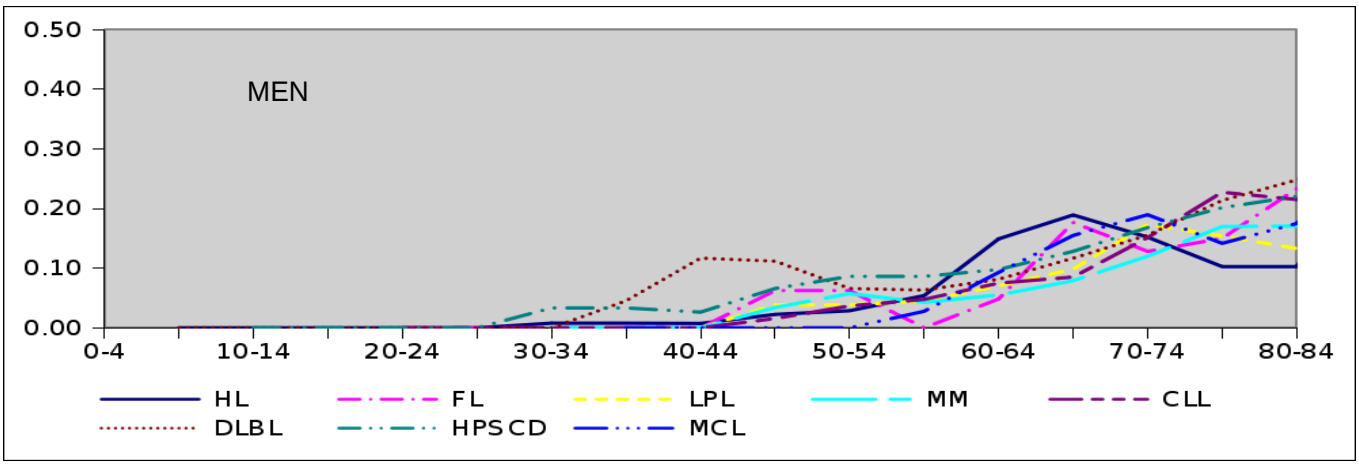


Figure 15: Incidence rate curves of associated solid malignancies before and after tumour of haematopoietic and lymphoid tissues, men and women (top), men (middle), women (bottom)
(x: age at diagnosis of tumour of haematopoietic and lymphoid tissues, y: incidence rate of solid AMN)





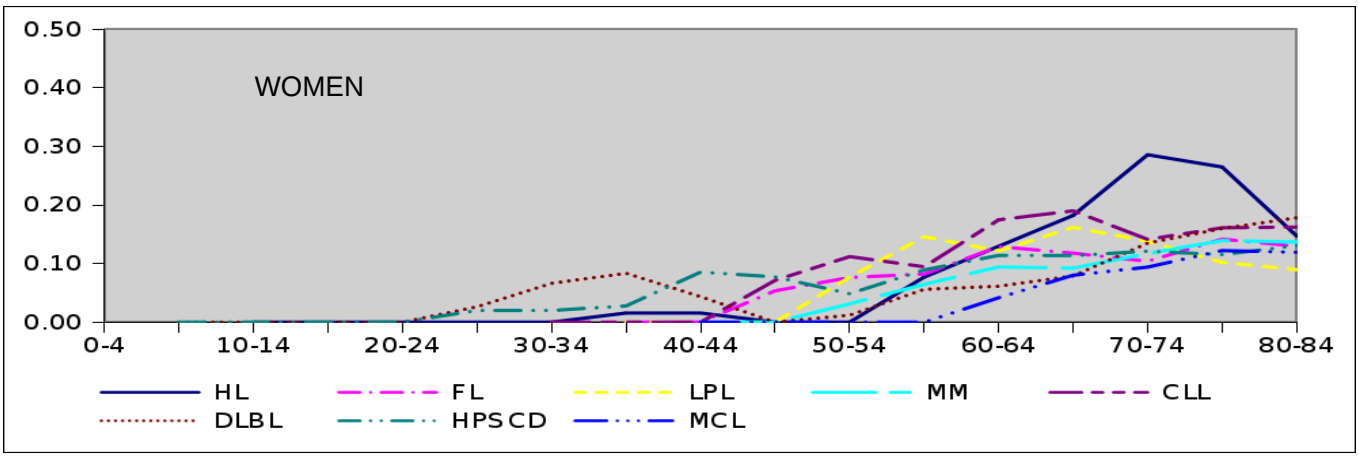
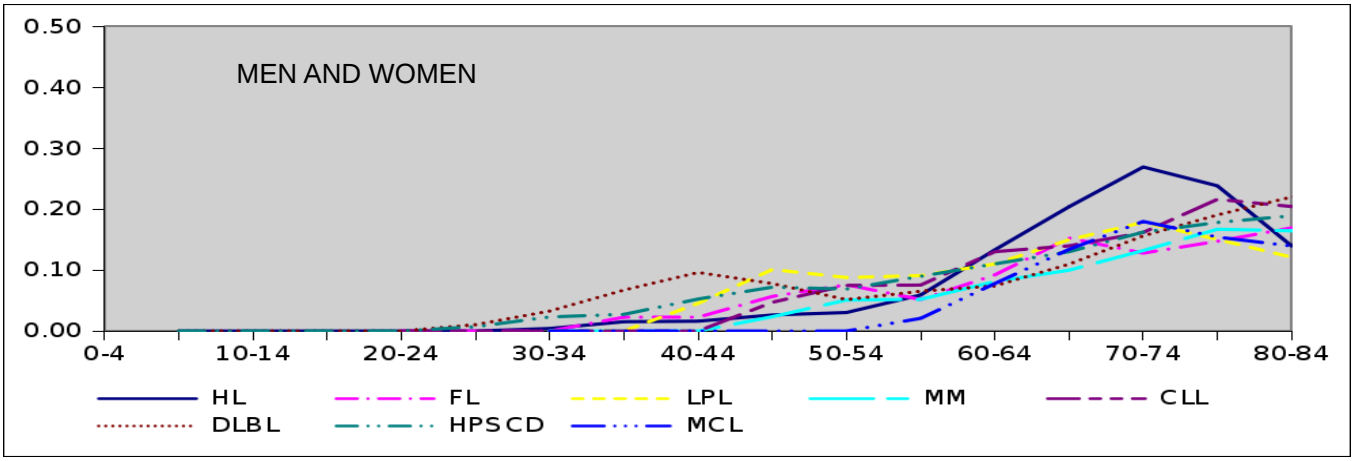
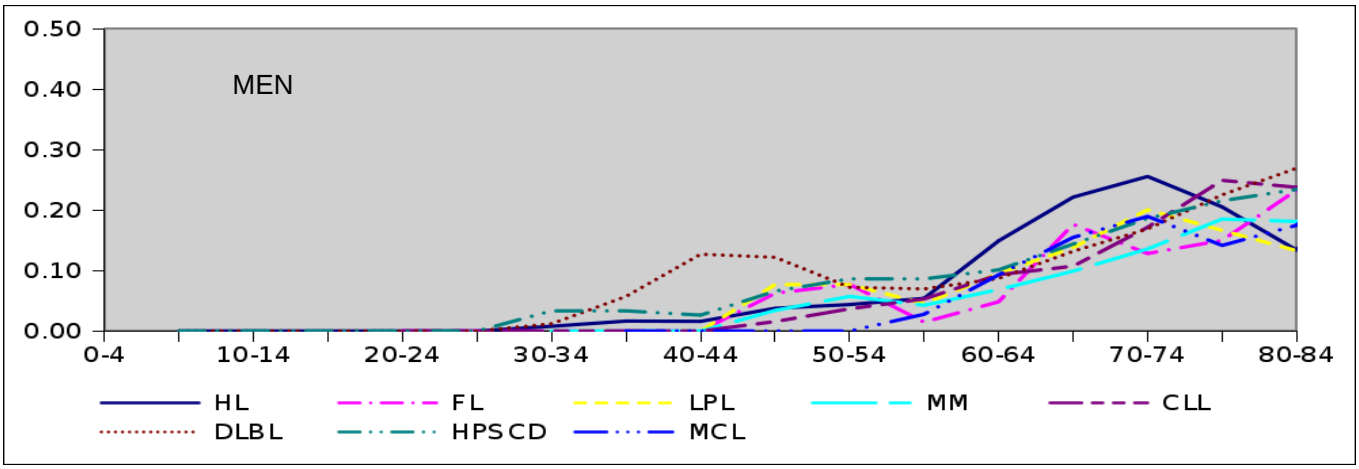


Figure 16: Incidence rate curves of associated solid malignancies before tumour of haematopoietic and lymphoid tissues, men and women (top), men (middle), women (bottom)
(x: age at diagnosis of tumour of haematopoietic and lymphoid tissues, y: incidence rate of solid AMN)





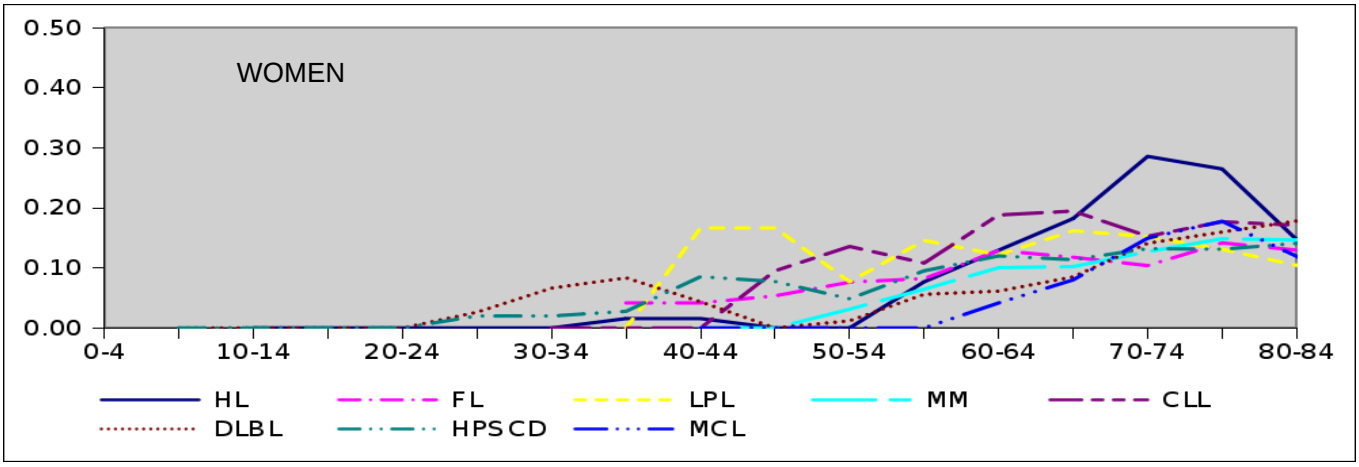


Figure 17: Incidence rate curves of associated solid malignancies before and 1 year after tumour of haematopoietic and lymphoid tissues, men and women (top), men (middle), women (bottom)
(x: age at diagnosis of tumour of haematopoietic and lymphoid tissues, y: incidence rate of solid AMN)

5.4.2 Statistical analyses for expected numbers of associated cancers using a generalized additive model for Poisson regression among seven selected groups MM, CLL, LPL, FL, DLBL, HL, HPSCD

Figure 18 shows the estimated mean numbers of AMN among women and men before tumour of haematopoietic and lymphoid tissues. The group specific analyses show the highest increase of estimated mean numbers of AMN in patients with HL in men and women.

Similar curves for expected numbers of associated cancers before and after tumour of haematopoietic and lymphoid tissues are included in the appendix.

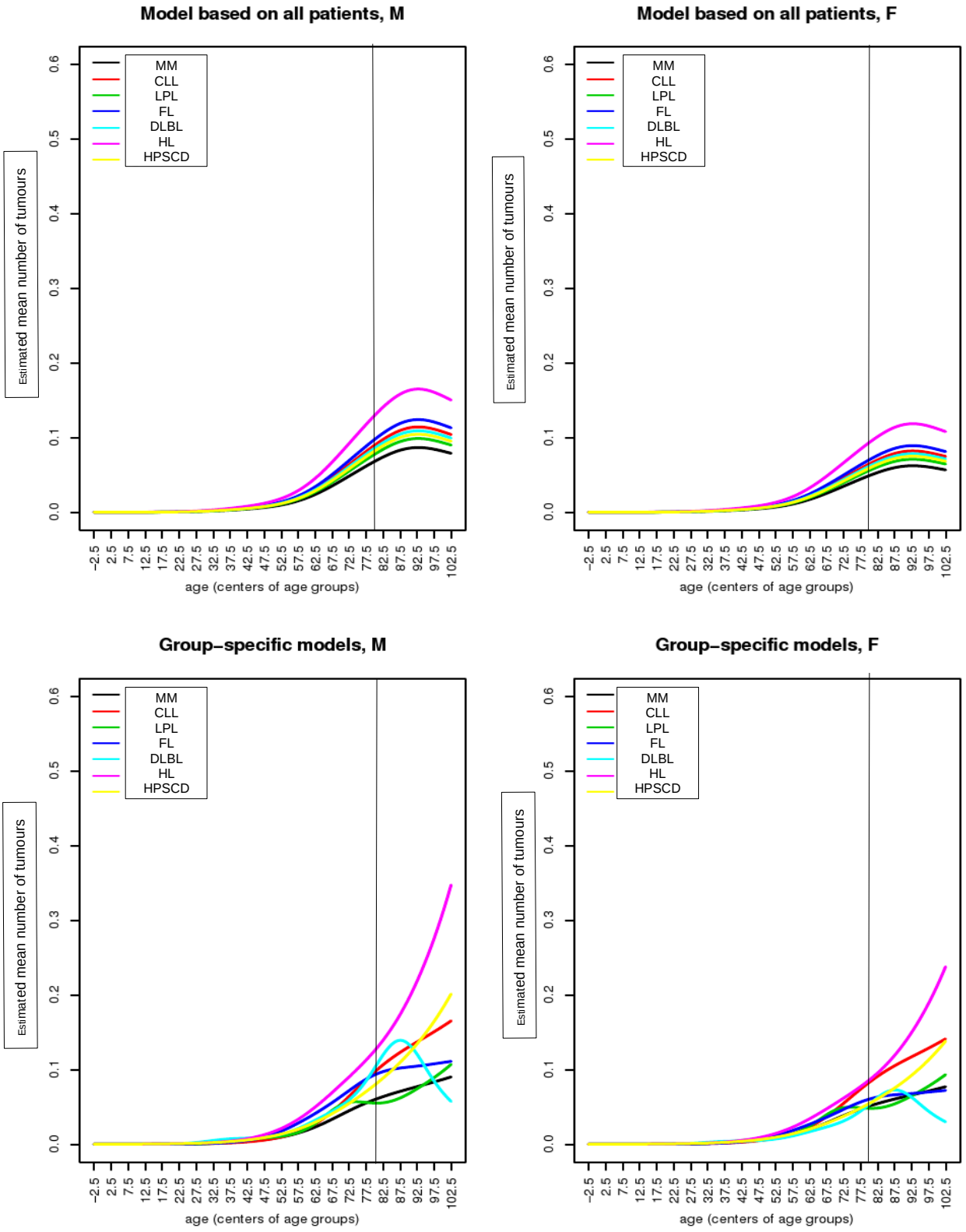


Figure 18: Expected numbers of associated cancers before tumour of haematopoietic and lymphoid tissues: joint model curves (top) and group specific curves (botttom) among women (right) and among men (left) [48]

5.4.3 Detailed analyses of the incidence rates among patients with HL

5.4.3.1 Age-specific incidence rates of associated solid malignancies in HL patients

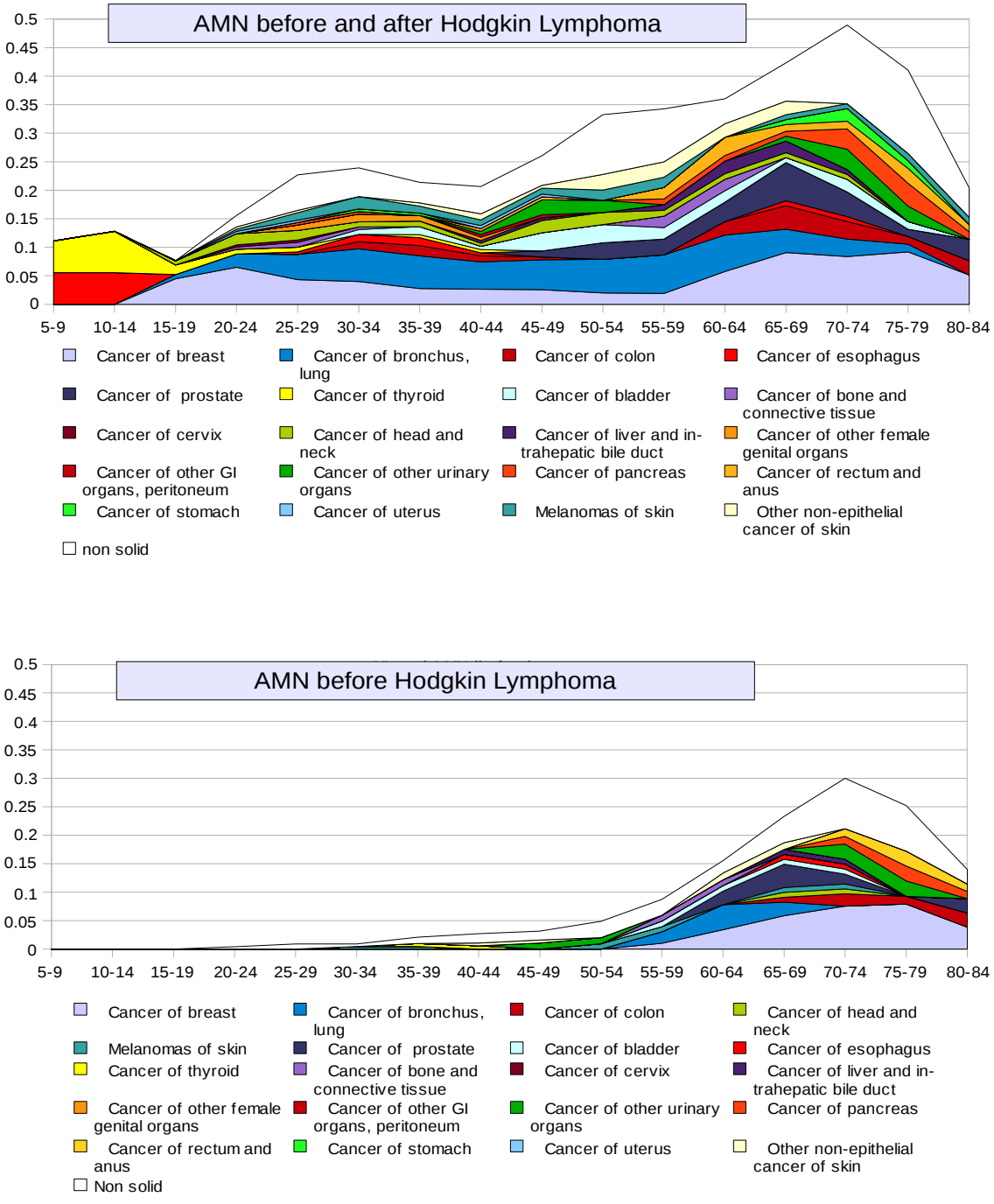


Figure 19: Age-specific incidence rates of associated malignancies: AMN before and after HL (top), AMN before HL (bottom), men and women *(x: age at diagnosis of HL, y: incidence rate of AMN)*

Because of the high incidence rate of AMN among HL we focused our next analyses on HL.

Figure 19 describes in detail the incidence rate curves of AMN before and after HL and AMN before HL. The x-axis shows the age at diagnosis of HL in 5 year intervall age groups in years. The y-axis shows the incidence rate of AMN in each age group.

The most prominently represented AMN among HL patients are cancer of breast, cancer of bronchus and lung, cancer of prostate, cancer of colorectum. Cancer of thyroid and cancer of oesophagus constitute the cases of AMN in childhood. Table 10 shows the exact numbers of the most represented AMN and AMN during childhood according to the age at diagnosis of HL, type of AMN and gender.

Solid AMN before and after HL																			
Name		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	**Total**
Cancer of breast		0	0	0	6	5	5	4	2	3	1	1	1	4	5	3	4	0	**44**
Cancer of bronchus and lung	M	0	0	0	0	2	2	6	5	3	3	3	3	2	2	1	0	0	**32**
	F	0	0	0	1	2	4	1	0	1	0	0	1	0	0	0	0	0	**10**
Cancer of colon, rectum and anus	M	0	0	0	0	0	0	2	1	2	0	0	2	2	1	2	0	0	**12**
	F	0	0	0	0	0	0	1	0	0	0	0	0	1	1	0	1	1	**5**
Cancer of prostate		0	0	0	0	0	0	0	0	0	1	2	1	2	5	0	1	1	**13**
Cancer of esophagus	M	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
	F	0	1	0	0	0	1	2	0	0	0	0	0	0	1	0	0	0	5
Cancer of thyroid	M	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	3
	F	0	0	0	0	1	0	0	1	0		0	0	0	0	0	0	0	2
Solid AMN before HL																			
Name		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	**Total**
Cancer of breast		0	0	0	0	0	0	0	0	0	0	0	1	2	4	3	3	0	**13**
Cancer of bronchus and lung	M	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	**3**
	F	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	**1**
Cancer of colon, rectum and anus	M	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	**3**
	F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	**2**
Cancer of prostate		0	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0	1	**5**
Cancer of esophagus	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	F	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Cancer of thyroid	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	F	0	0	0	0	0	0	0	1	0		0	0	0	0	0	0	0	1

Table 10: Numbers of the most prominently represented solid AMN (black) in adults and solid AMN in childhood (grey) solid AMN according to the age of diagnosis of HL, type of AMN and gender.

5.4.3.2 Age-and gender-specific incidence rates of associated solid malignancies among all tumours of haematopoietic and lymphoid tissues and HL

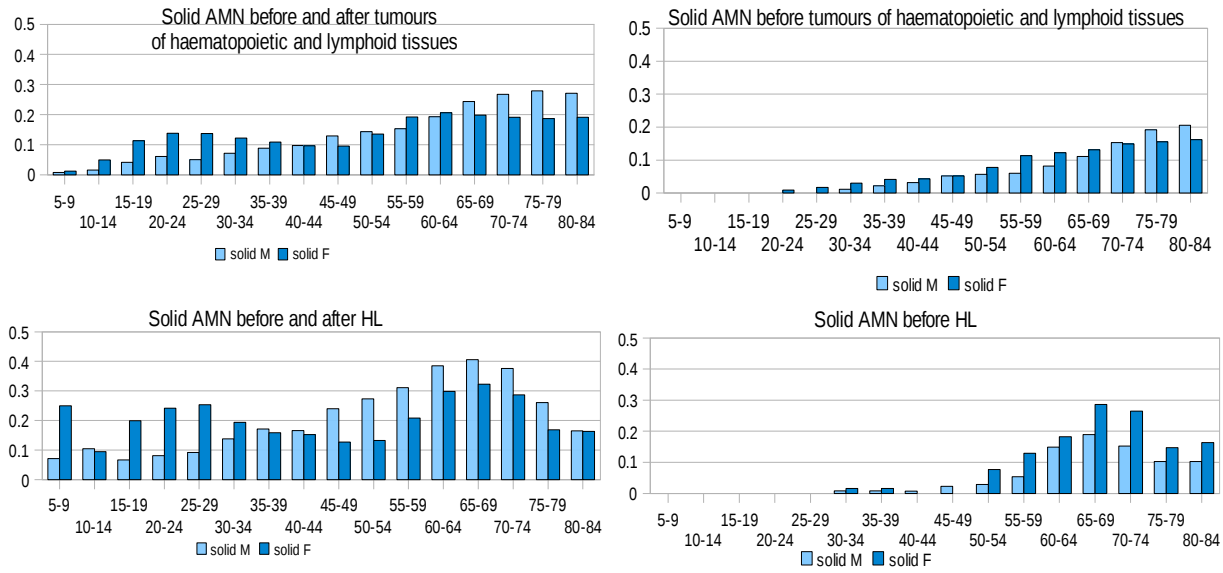


Figure 20: Age-and gender-specific incidence rates of solid AMN: before and after all tumours of haematopoietic and lymphoid tissues or HL (left); before all tumours of haematopoietic and lymphoid tissues or HL (right) *(x: age at diagnosis of tumour of haematopoietic and lymphoid tissues, y: incidence rate of solid AMN)*

Figure 20 shows the age-and gender-specific incidence rates of solid AMN. We compared the incidence rates of solid AMN in all patients with tumours of haematopoietic and lymphoid tissues with solid AMN in HL patients. Figure 20 shows the incidence rates of solid AMN among men and women before and after all tumours of haematopoietic and lymphoid tissues or HL as well as before all tumours of haematopoietic and lymphoid tissues or HL. The x-axis shows the age at diagnosis of HL in 5 year intervall age groups in years. The y-axis shows the incidence rates in each age group among men and women.

Figure 20 shows that up to 25% of women with HL diagnosed between 20 and 30 years old developed a previous or subsequent solid cancer in the study period from 1980 and 2008 (versus 14% in all patients with tumour of haematopoietic and lymphoid tissues in the 25-29 year old group). Furthermore almost 30% of women with HL diagnosed between 65 and 74 years old had a previous solid AMN in the study period from 1980 and 2008 (versus 13% in all patients with tumour of haematopoietic and lymphoid tissues in the 65-69 year old group).
The RR of previous solid malignant neoplasm in HL patients compared to all patients with tumours of haematopoietic and lymphoid tissues (except HL) diagnosed between 65 and 69 years old is 2,29 among women and 1,31 among men.

5.4.3.3 Age-and gender-specific incidence rates of cancer of breast, prostate, bronchus and lung as well as colon, among all tumours of haematopoietic and lymphoid tissues and HL

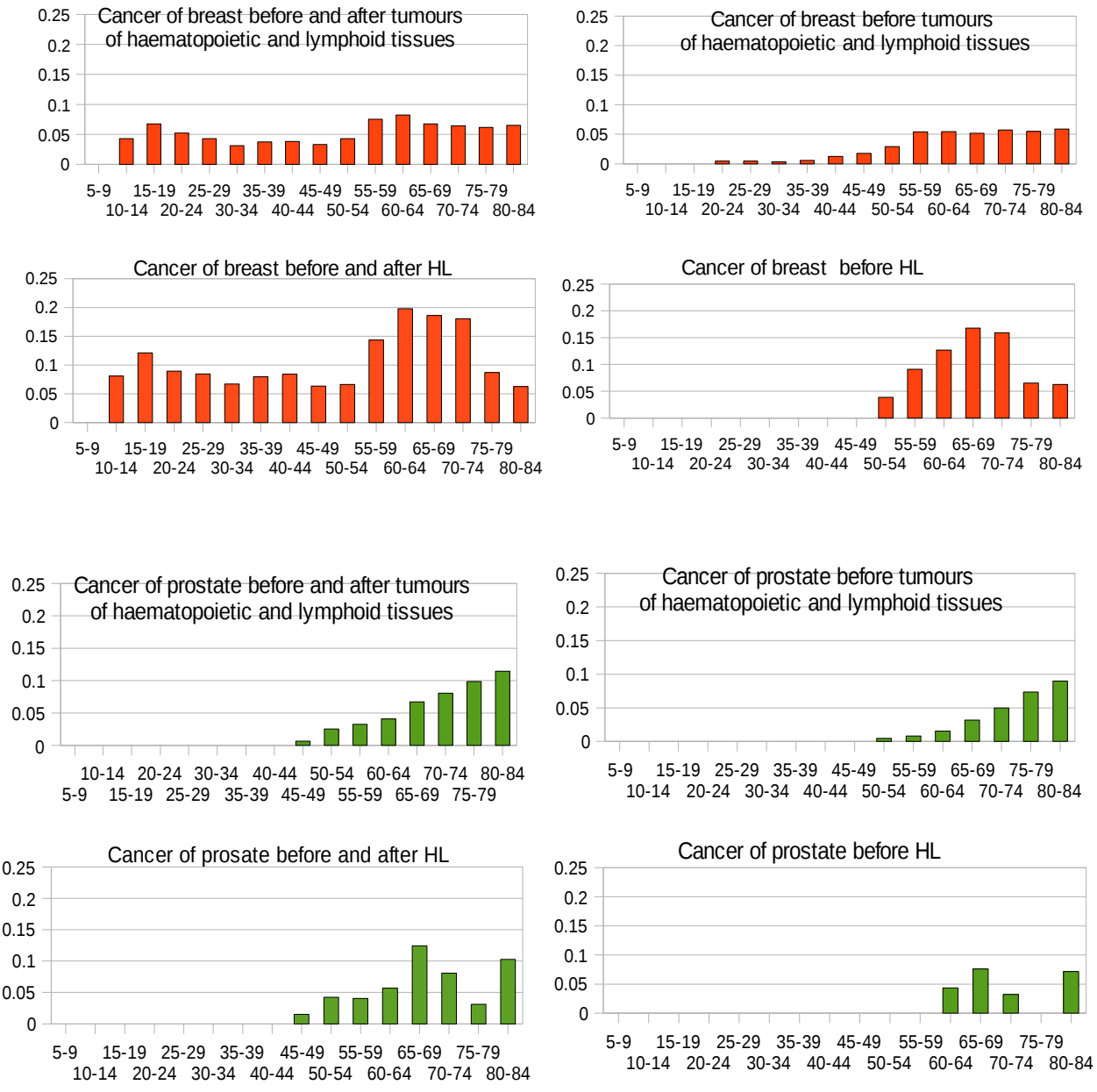


Figure 21 a: Age-and gender-specific incidence rates of cancer of breast and prostate: before and after all tumours of haematopoietic and lymphoid tissues or HL (left) and before all tumours of haematopoietic and lymphoid tissues or HL (right) *(x: age at diagnosis of tumour of haematopoietic and lymphoid tissues y: incidence rate of a specific AMN)*

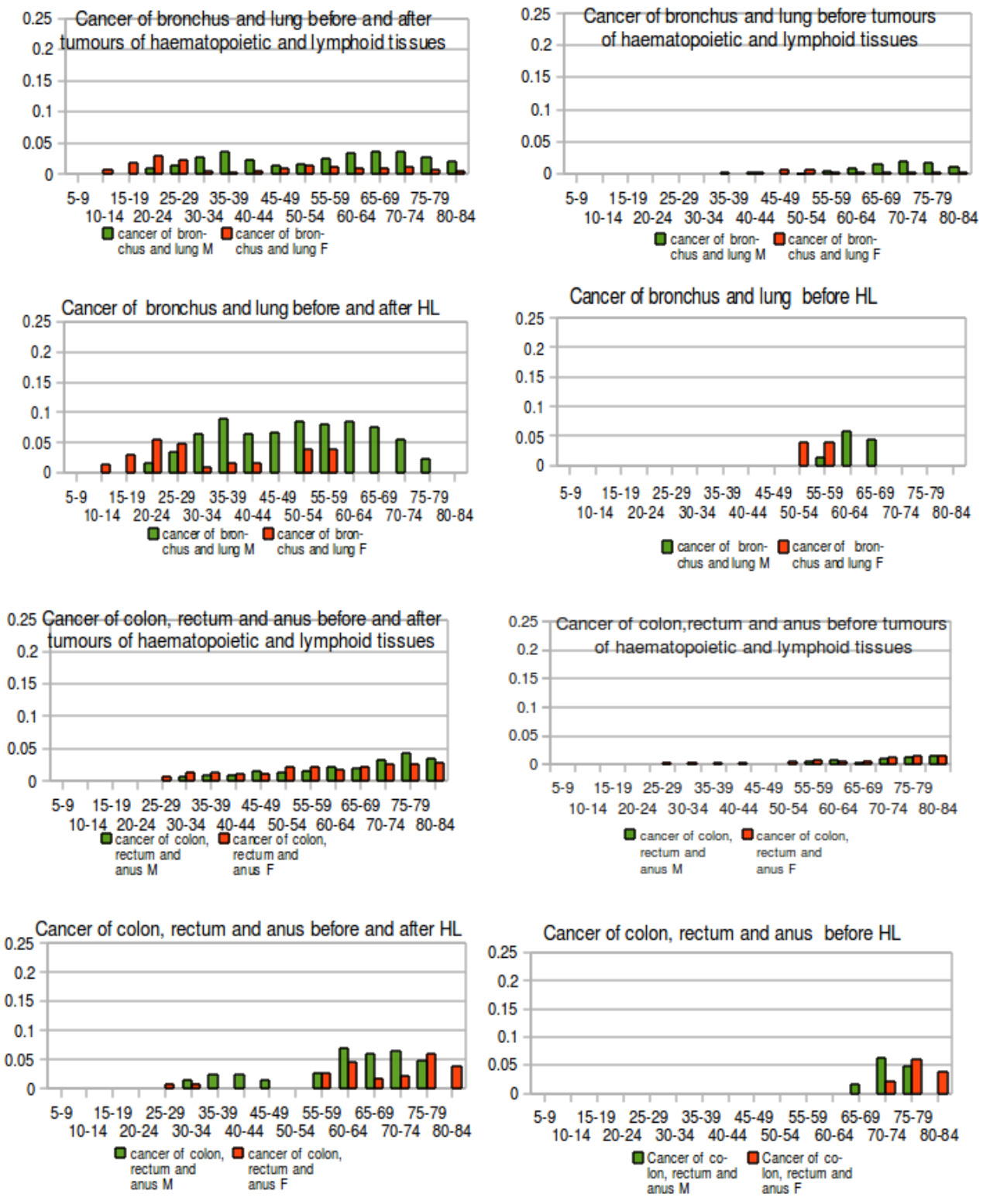


Figure 22 b: Age-and gender-specific incidence rates of cancer of bronchus and lung as well as colorectum: before and after all tumours of haematopoietic and lymphoid tissues or HL (left) and before all tumours of haematopoietic and lymphoid tissues or HL (right) *(x: age at diagnosis of tumour of haematopoietic and lymphoid tissues , y: incidence rate of a specific AMN)*

Figure 21 shows the age-and gender-specific incidence rates of cancer of breast, cancer of prostate, cancer of bronchus and lung and cancer of colonrectum (colon, rectum and anus). We compared incidence rates of the specific solid AMN among all patients with tumours of haematopoietic and lymphoid tissues with incidence rates of the specific solid AMN among HL patients.

Figure 21a shows that most of AMN before HL are breast cancers. 17% of women with HL diagnosed between 65 and 69 years old had a previous cancer of breast in the study period from 1980 and 2008 (versus 4% in all women with tumours of haematopoietic and lymphoid tissues diagnosed between 65 and 69 years old).
The RR of previous breast cancer in HL compared to all other tumours of haematopoietic and lymphoid tissues (except HL) diagnosed between 65 and 69 years old is 3,80.

5.5 Age-and time period specific incidence rates of AMN among patients with Hodgkin lymphomas

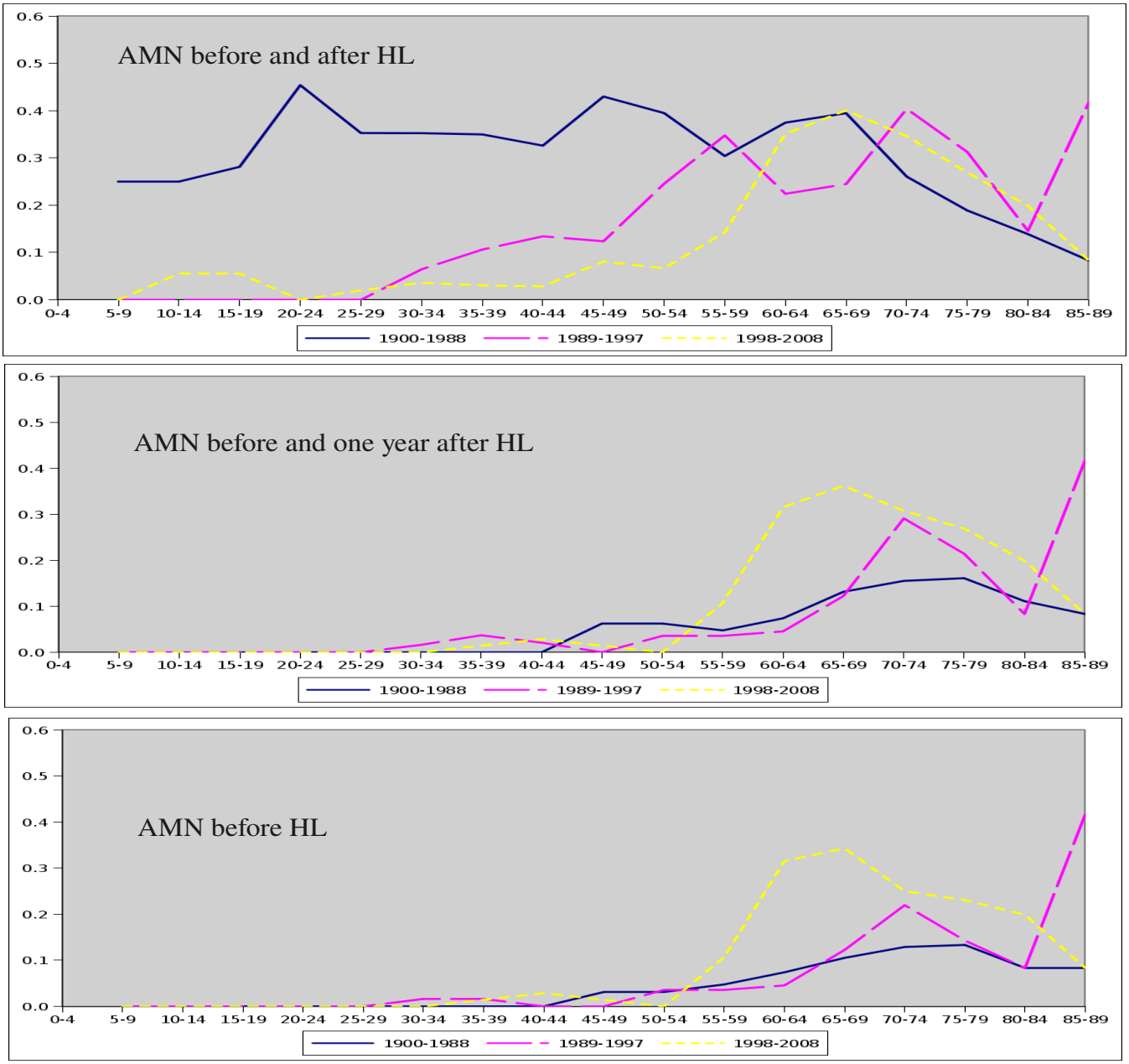


Figure 23: Age- and time period specific incidence rate curves of solid AMN before and after HL (top), before and 1 year after HL (middle) and before HL(bottom), men and women
(x: age at diagnosis of HL, y: incidence rate of solid AMN)

Figure 23 shows the incidence rate curves of solid AMN according to the age and date of diagnosis of HL. We divided the period from 1980 to 2008 into 3 periods for comparison.
In the time period between 1998 and 2008 AMN are mostly diagnosed before HL. The patients diagnosed between 1998 and 2008 had less time (at the time of the study) to develop subsequent AMN compared to patients diagnosed in 1989-1997 and 1900-1988.

6 Discussion

6.1 Numbers of patients, tumours of haematopoietic and lymphoid tissues and AMN

We analysed a population of 12'798 patients with tumours of haematopoietic and lymphoid tissues collected in the population based cancer registry of the Canton of Zurich over a period of 28 years and found 2'885 associated cancers. After excluding patients with more than one cancer of haematopoietic and lymphoid tissues, we detected 2'374 previous and subsequent AMN in 10'923 patients.

We found a significant number of associated malignant neoplasms after tumours of haematopoietic and lymphoid tissues. Our study is seminal in that we also investigated the inverse case, whether special types of hematopoietic and lymphoid malignancies are preceded by an increased number of previous cancers.

Other studies have previously analysed cancers associated with hematopoietic and lymphoid malignancies [1]-[22][42][43][49]. Some of these reports are summarized in the Table 2 in the introduction. Some studies include databases of population based cancer registries [1][3][5][6] [10][11][13]-[15][17]-[19][43][49] or databases of specific institutions like Late Effect Study Group member institutions in the study group of Bhatia et al. [1]. Some studies cover a patient database of one or several given hospitals [4][7][8][12][16][20]-[22][42]. The advantages of a population based study is to have exact and extensive health-related parameters. Population based studies rarely contain biases as they are representative of a given population [50].

Therefore, we consider it a strength of our study that the data was extracted from a population based cancer registry. Our results are representative for a population of 1.3 million people in Western Europe [44][45].

Some studies have analysed patients with HL [1]-[9]. The highest population number was 32'591 patients suffering from HL in the study of Dores et al [3]. In 2002 they discoverd 2'153 secondary malignancies over a 25 year period in 16 population-based cancer registries in North America and Europe [3]. The smallest analysis was conducted by the study group of Foss Abrahamsen et al. In 2002 and they discovered 197 secondary malignancies among 1'024 HL patients [4]. From 1968 to 1985 they included patients at the beginning of their treatment of HL at the Norwegian Radium Hospital and followed them for second malignancies from 1969 through 1998 in the Norwegian Cancer Registry [4]. Some other studies covered patients with other tumours of haematopoietic and lymphoid tissues other than HL [10]-[22][42][43][49]. For example, Hisada et al. analysed 358 second cancers in 3'104 hairy cell leukaemia survivors, in 16 population-based registries in the Surveillance, Epidemiology and End Results (SEER) Programme between 1973 and 2002 [13].

However, few studies mentioned previous and concomitant neoplasms in patients with HL [23].
The higher incidence of malignancies in our study in comparison to the above mentioned studies is due to differences in the studied population. We analysed associated malignancies in all patients with tumours of haematopoietic and lymphoid tissues. That included a majority of older patients in whom the rate of malignancy is already high independently of tumours of haematopoietic and lymphoid tissues. The studies which analysed patients with HL [1]-[9] limited themselves to patients with HL which is a disease of younger people who have an inherently lower baseline cancer rate at young age. We also analysed both previous and subsequent AMN. Our numbers therefore tend to be higher than those of studies that focused or were limited on subsequent AMN [1]-[22][42][43][49].

6.2 Average age and sex ratio of patients with AMN

Our data shows an increased incidence rate of AMN in the older population with haematopoietic and lymphoid cancer. As already mentioned, this is concordant with the higher incidence of cancers in elderly persons [51].

For some subtypes of tumours of haematopoietic and lymphoid tissues, the incidence rate of AMN changed after the age of 80 years. This change can partly be explained by less stringent medical procedures to establish a diagnosis in the population aged above 80 years.

We found more men than women with AMN. This is in line with the higher incidence of solid and non solid cancer in men [51].

6.3 Numbers of AMN per thousand tumours of haematopoietic and lymphoid tissues in patients with AMN

We found that indolent B cell lymphomas and HL (237cases/1'000 for both) showed the highest number of AMN, both for previous and subsequent cancers. HL are diagnosed at an early age and have an excellent survival. Indolent B cell lymphomas, though diagnosed later in life also show an excellent survival. Therefore more patients are at risk for the development of AMN compared to other tumours of haematopoietic and lymphoid tissues with a shorter survival rate [24].

For other tumours of haematopoietic and lymphoid tissues the incidence of AMN per thousand tumours of haematopoietic and lymphoid tissues is low. This is the case with aggressive B cell lymphomas (178/1'000), MM (169/1'000) and ALL (81/1'000), which all show higher mortality rates and shorter survival rates than patients with HL and indolent B cell lymphomas [24].

Some diagnoses of tumours of haematopoietic and lymphoid tissues show excessively high numbers of AMN. These include cancers with lower incidence and therefore fewer registered patients. These are namely extramedullary plasmocytoma (324/1'000), AILT (271/1'000), lymphohistiocytic sarcoma (381/1'000) and LDHL (303/1'000). Some of these associations may be due to duplicate coding, such as extramedullary plasmocytoma and MM. Others may be representing artefacts of low numbers or they may represent a true feature of the specific tumour of haematopoietic and lymphoid tissues.

6.4 Incidence rates of associated malignant neoplasms

We found a significant number of AMN before and after tumours of haematopoietic and lymphoid tissues, especially HL. Our study is concordant with previous studies also showing an increased risk of associated cancer after tumours of haematopoietic and lymphoid tissues, especially childhood HL [1]-[9].

Our analyses show that the most frequent solid cancer preceding HL is breast cancer. The RR of previous breast cancer in HL compared to all patients with other tumours of haematopoietic and lymphoid tissues (except HL) diagnosed between 65 and 69 years old is 3,80. Cancers of the lung, colorectum or prostate are also more frequently preceding HL in comparison to other tumours of haematopoietic and lymphoid tissues. These cancers however precede less frequently HL than breast cancers do (13 cases of breast cancers versus 5 cases of prostate cancers, 5 cases of colorectal cancers and 4 cases of lung cancers). The numbers are too small for meaningful statistical comparison. These associated solid cancers represent the commonest cancers in the general population in Switzerland [44].

The finding that HL is more frequently preceded by breast cancer is striking and calling for an explanation. We therefore reviewed the literature for previous reports of an increased incidence of HL among breast cancer survivors.

6.5 Incidence rates of associated malignant neoplasms in HL patients

6.5.1 HL among breast cancer survivors

n the literature some studies analyzed the risk of developing secondary malignancies after breast cancer [52]-[55]. A Swiss study included 9'729 breast cancer patients registered by the cancer registries of Vaud and Neuchâtel (covering about 786'000 inhabitants), with a follow up from 1974 to 1998 [53]. They described an increased standardized incidence ratio (SIR) of 1.38 for NHL (95% CI 0.84–2.13), 0.68 for MM (95% CI 0.22–1.58) and 1.20 for leukaemias (95% CI 0.66–2.02) [53]. No increased SIR was described for HL in the study. A second study identified a cohort of 525'527 women with primary breast cancer from 13 population-based cancer registries in Europe, Canada, Australia and Singapore. The study group followed these women for secondary cancers within the period 1943-2000 [54]. The highest SIR of secondary non breast cancers were cancers of the stomach, the colorectum and the lung, soft tissue sarcomas, melanomas, non-melanoma skin cancers, endometrium, ovary, kidney, thyroid gland cancers and leukaemia. The SIR of developing a secondary cancer after breast cancer was less significant for NHL and not significant for HL [54]. A third study analyzed a total of 145'677 Swedish women with breast cancer diagnosed between 1961 and 1995. No significant increase of the incidences of NHL, MM, lymphoid leukaemia after breast cancer was shown. But an increased incidence of myeloid leukaemia (breast cancer diagnosed at age < 50, SIR of 2.31 with CI 1.52-3.51) could be shown [55]. In conclusion cases of non solid malignancies following breast cancer have been described in the literature but they are not as predominantly represented as solid cancers.

We also reviewed common etiological factors which could induce HL and cancers of the breast, lung, prostate or colorectum in order to explain our results.

6.5.2 Common etiological factors of HL and cancers of the breast, lung, prostate or colorectum

6.5.2.1 Genetic factors and tumours of haematopoietic and lymphoid tissues

A multicentric case control study from Sweden and Denmark compared the risk of secondary cancers associated with a family history of any cancer in patients with HL. They observed an isolated increased relative risk (1.81, 95% CI 1.04–3.16) of breast cancer as a secondary malignancy among HL patient with positive (versus negative) family history of cancer. The increased risks of breast cancer among HL patients with positive family history of any cancer suggests in part a common genetic factor [56]. Though, the idea of common genetic factors between HL and breast cancer is controversial in the literature. On one hand, genetic mutations of TP53, BRCA1, BRCA2 and ataxia telangiectasia genes were not frequently observed in cohorts of HL patients developing secondary malignant neoplasms [57][58]. On the other hand, a meta analysis concluded that an intact BRCA1 and 2 pathway protects from haematologic cancer in addition to breast and ovarian cancers [59]. A genetic defect in the BRCA pathway increases the risk of developing haematologic cancers up to nearly 2000 fold for certain leukemias and lymphomas (mostly MCL, AML, ALL, CLL and LPL). An increased risk of HL was not observed [59]. Finally we found no clear common genetic etiological factors in the literature,

which could explain the increased incidence rate of breast cancer preceding HL.

No common genetic risk factors are found in the literature between HL and cancer of lung. Secondary p53 mutations following radiotherapy in HL patients may cause some radiation-induced cancers like lung cancers [60].

6.5.2.2 Lifestyle and occupational exposure and tumours of haematopoietic and lymphoid tissues

The role of tobacco in the carcinogenesis is well established in lung cancer patients. Its role seems to be stronger in HL (however not always statistically significant) compared to NHL [61]. Increased risk after tobacco exposure has also been described for specific NHL, namely FL among women [61][61]. On the one hand some studies have reported a significantly higher risk of secondary lung cancers in HL patients among smokers compared to non smokers and on the other hand others have not found an higher risk [63].

In our study we analysed incidence rates of lymphoma subtypes and tobacco-induced cancers (especially cancers of the head, neck and the bladder). We did not find an increased incidence of tobacco-induced cancers other than lung cancer, especially among HL and FL patients.

A causal association between exposure to benzene and an increased risk of leukaemia is well-established, as well as a presumptive risk of lung cancer [64]. In addition to NHL and prostate cancer several others cancers may be linked to a variety of pesticides (namely cancers of the breast, the colorectum, the lung) [65]. But no chemical substances (e.g. solvents, pesticides) are known according to literature to increase the incidence of HL and cancers of the prostate, lung, breast and colorectum.

We found no common environmental etiological factors in the literature which could explain the increased incidence of breast cancer preceding HL.

6.5.2.3 Immunosuppression and tumours of haematopoietic and lymphoid tissues

Among HIV patients increased incidences of HL (RR 11.5, 95% CI 10.6-12.5) and lung cancer (RR 4.5, 95% CI 4.2-4.8) have been observed in the USA suggesting a potential association of these two cancers with immunosuppression [66]. However, lung cancer may have occurred in excess in persons with HIV/AIDS because of heavy smoking [66].

Ulcerative colitis patients are at an increased risk of colorectal, hepatobiliary, non melanoma skin cancers and acute myeloid leukaemia. An increased risk of HL was not observed among ulcerative colitis patients [67].

The majority of malignancies after blood or marrow stem-cell transplantation are NHL, HL or solid tumours, namely melanoma, brain, and oral cavity tumours [68][69]. The literature does not indicate a significantly increased incidence of cancer of the breast, the lung, the colorectum and the prostate after blood or marrow stem-cell transplantation.

The most frequent cancers after organ transplantation are malignant lymphomas and cutaneous neoplasms [70]. The observed incidence rates of malignancies in patients after transplantation range from 4.1% to 16% in different series. Although a decreased incidence of breast cancers has been reported after organ transplantation in the literature, there is contradictory data concerning the incidence of breast cancer in those patients compared with the overall population [70].

Tumour-mediated immunosuppression following breast, lung, colorectal and prostate cancer, may represent an etiological factor and induce hypothetically an adequate environment for HL, but review of the literature shows that evidence in supporting this hypothesis is limited. In comparison with renal cell carcinoma or melanomas considered as highly immunogenic, breast cancer is a weak immunogenic tumor [71]. Colorectal [72] and prostate cancers [73] are potentially immunogenic. The clinical research in this domain is however still under development [74].
We found no common immunological etiological factors in the literature which could explain the increased incidence of breast cancer preceding HL.

6.5.2.4 Infection and tumours of haematopoietic and lymphoid tissues

Parallel to its established causal association with both infectious mononucleosis and young adulthood HL, a descriptive and a population based case control study [75] proposed a hypothesis in 2001 that “delayed” primary EBV infection (i.e., primary infection occurring during adolescence or adulthood) is associated with an elevated risk of developing breast cancer. Using an international/United States cancer registry data, they observed similarities between incidence rates among women of young adulthood HL (mostly nodular sclerosis subtype), “delayed” primary EBV infection and breast cancer. The analytical study analysed the age adjusted ratio of breast cancers in women who reported a history of early or late infectious mononucleosis (odds ratio of breast cancer in women with early infection (0-9 years of age) of 0.55 versus 2.67 in women with late infection (>25 years of age)) [75]. A “delayed” EBV infection thus may be an etiological factor for HL and breast cancer. Another study published in 2008 analysed the breast cancer risk in association with microbial cancer (cervical, liver and stomach cancers associated with HPV, hepatitis viruses and helicobacter pylori) in 74 women populations around the world. Their deducted hypothesis was that breast cancer etiology may have an appreciable link with microbial exposure (and/or immunological response to them). The lack of microbial exposure, especially in early life, may elevate breast cancer risk [76]. Our data however does not allow for an interpretation of these studies.

6.5.2.5 Therapy and tumours of haematopoietic and lymphoid tissues

Therapy of breast cancer like breast irradiation, adjuvant chemotherapy, and tamoxifen treatment is associated with an increased risk of secondary cancers that may manifest decades later. Chemotherapy with alkylating agents (e.g. cyclophosphamide), topoisomerase II inhibitors and antracycline antibiotics (doxorubicin and epirubicin) can be associated with leukaemias [77]. HL could be hypothetically the complication of the treatment of breast and lung cancer (alkylating agents, topoisomerase inhibitors and radiotherapy). In the literature no clear evidence showed a direct association between breast cancer therapy and occurrence of following HL. Moreover, other tumours of haematopoietic and lymphoid tissues like AML that are known to be increased after such therapies, were not found to be increased in our study.

6.6 Clinical implications

Because of the remarkable gains in survival attributable to successful treatment of HL, secondary malignancies are actually the leading cause of death among HL survivors. In the literature, the necessity of long term follow-up screening programs among young HL survivors are well documented [78][79]. Our findings suggest that when HL is diagnosed in an older person, a search for concomitant immunomodulation such as caused by an auto-immune disease or a secondary cancer must be undertaken. Moreover enlarged lymph nodes among breast cancer survivors may also represent the manifestation of HL.

7 Conclusion

We show herein for the first time that HL are not only associated with later malignancies but that they are also associated with previous malignant neoplasms, mostly breast cancer and less significantly cancers of the lung, the colorectum and the prostate. The reason for this association of previous malignant tumours with later HL may include common genetic risk factors, direct genotoxic therapy effects and immunomodulation due to therapy or due to the cancer itself. In the literature, the only clear common etiological factor is a delayed EBV infection which could induce both HL and breast cancer. Further studies could therefore include investigation of EBV states in both HL and breast cancer patients. Moreover analyses with more patients must be undertaken to confirm the data. Our study may prompt for a systematic search for solid cancers in patients diagnosed with HL at an advanced age.

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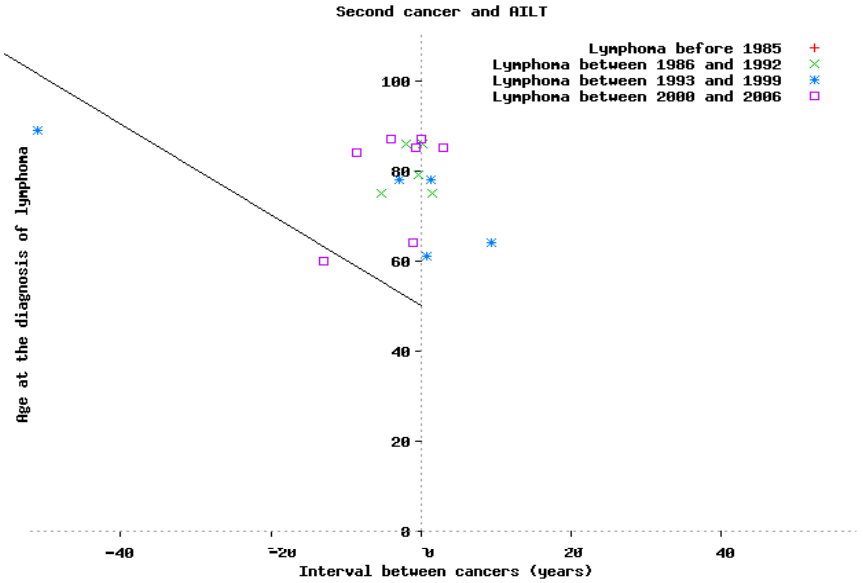
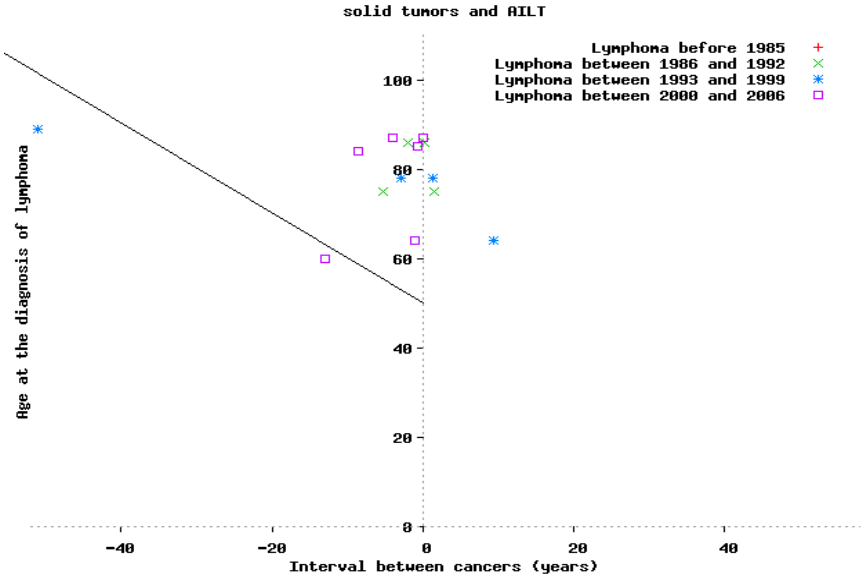
9 Appendix

9.1 Scatter diagrams

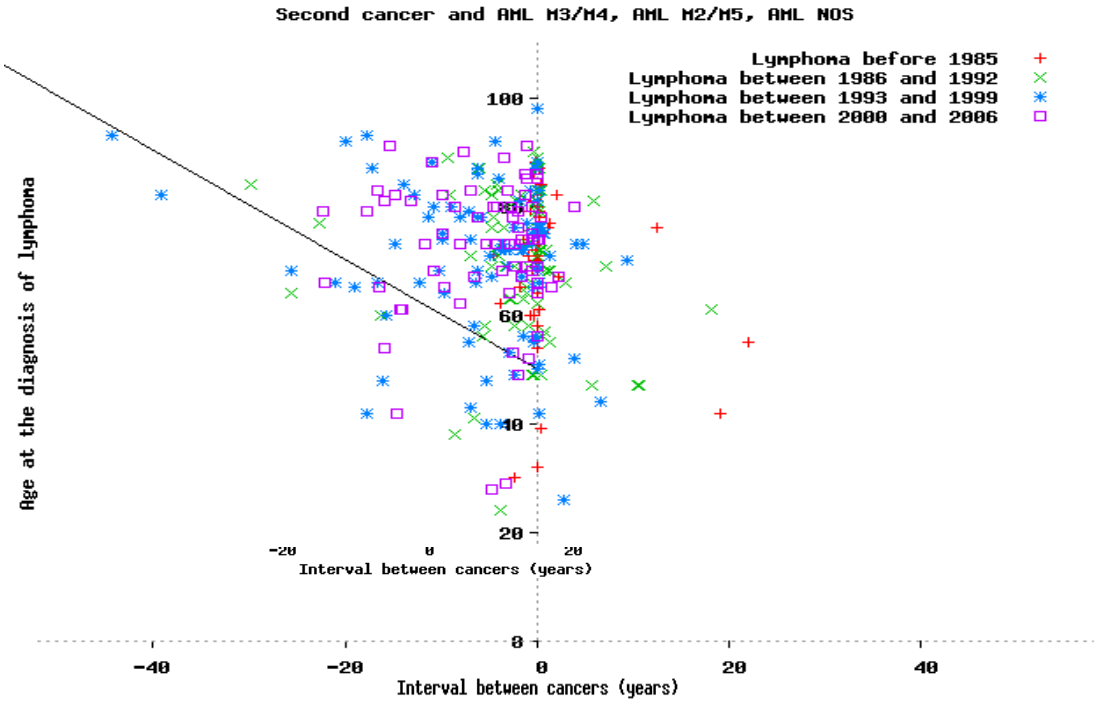
The next figures show, in alphabetic order, scatter diagrams of subtypes of lymphohaematopoietic cancers and their associated malignancies. The x-axis shows the time interval between the tumour of haematopoietic and lymphoid tissues and the associated cancer in years. The y-axis shows age at diagnosis of lymphohaematopoietic cancer in years. Furthermore calendar years of diagnosis of the lymphohaematopoietic cancer are indicated with different symbols (in the legend). There are shown two figures per subtype of tumour of haematopoietic and lymphoid tissues. The first figure shows all associated cancers (solid and non solid cancers) and the subtype of lymphohaematopoietic cancer. The second figure shows solid associated cancer and the subtype of lymphohaematopoietic cancer.

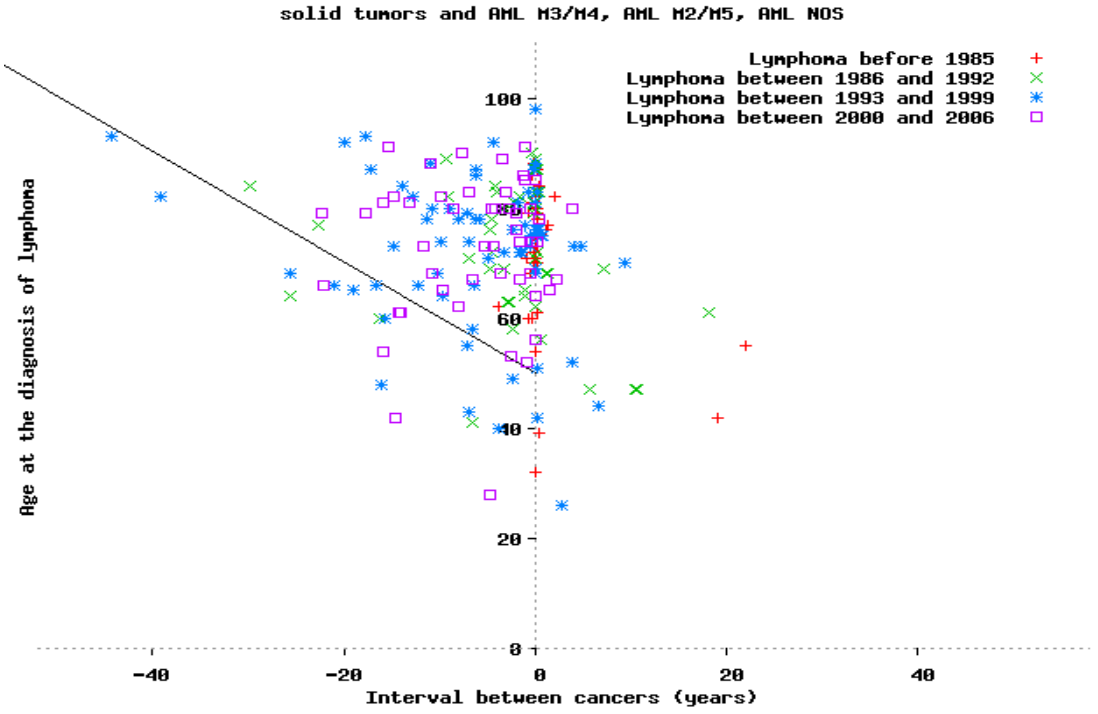
9.1.1 Associated cancers and AILT



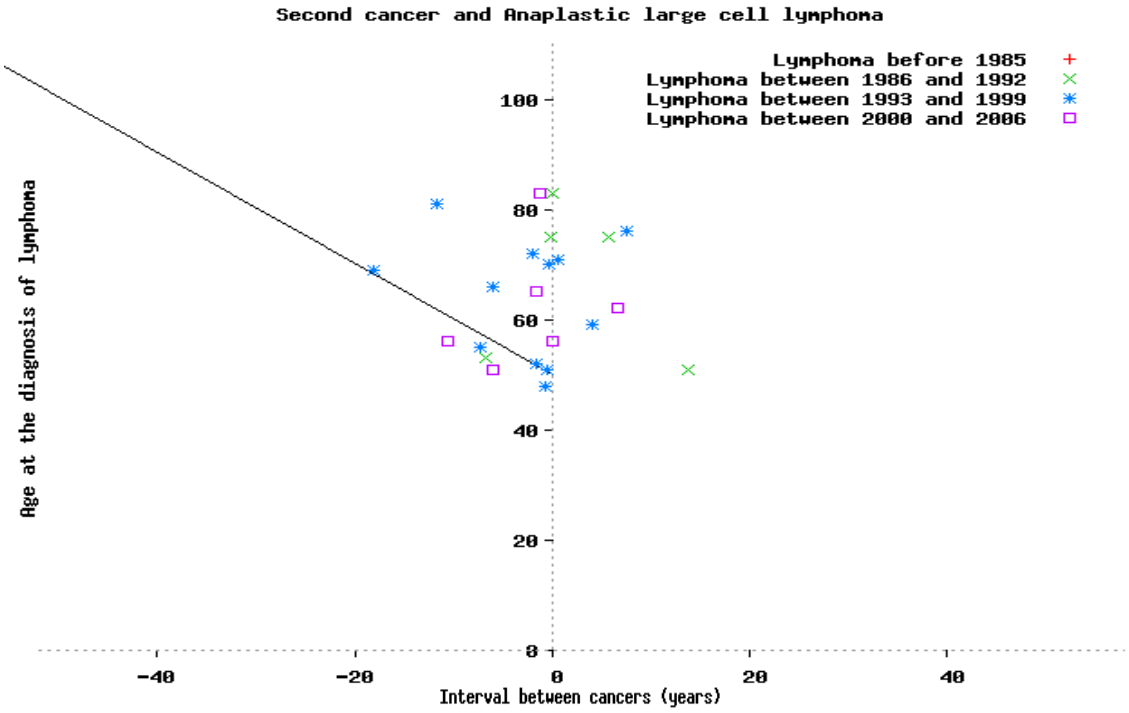


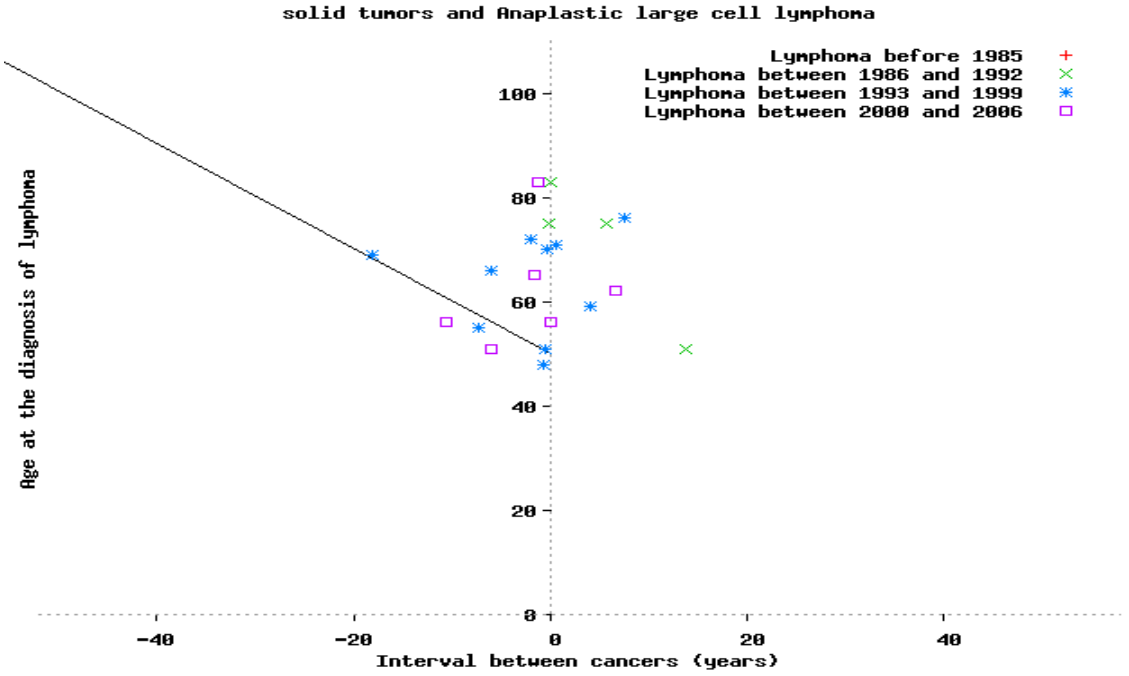
9.1.2 Associated cancers and AML



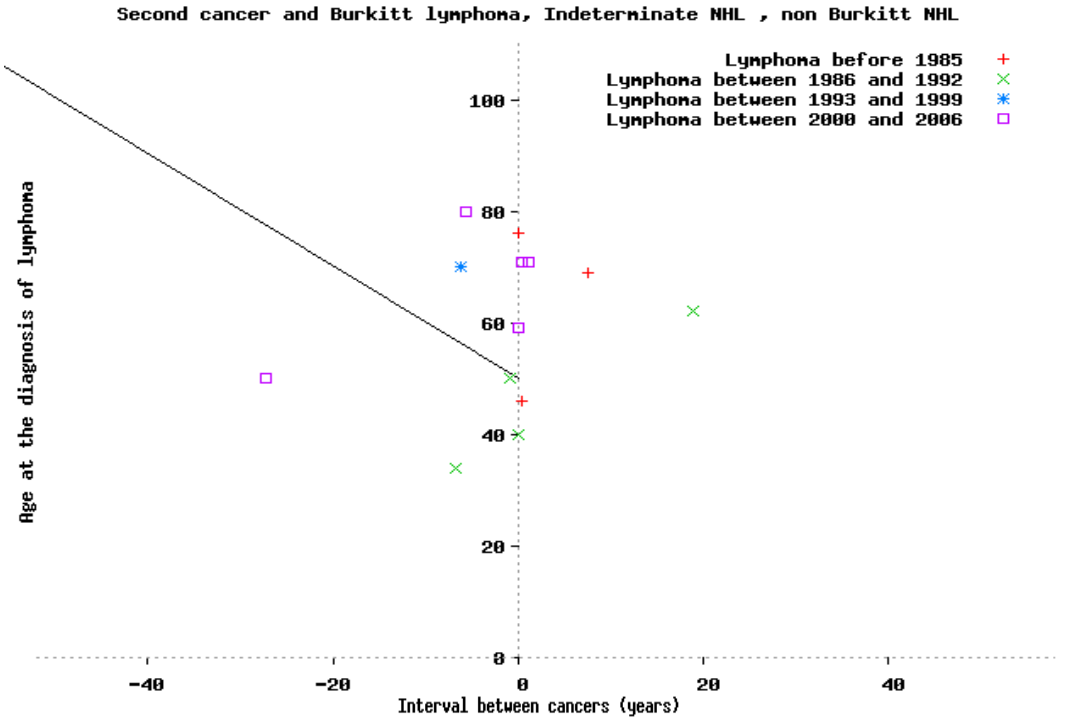


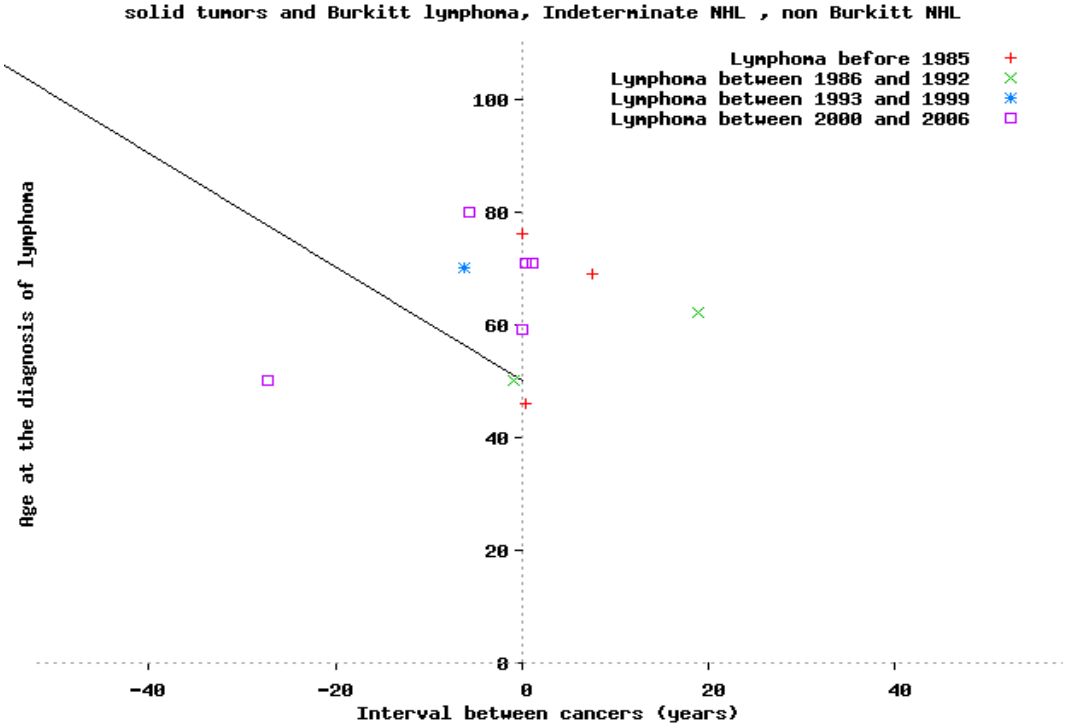
9.1.3 Associated cancers and anaplastic large cell lymphoma



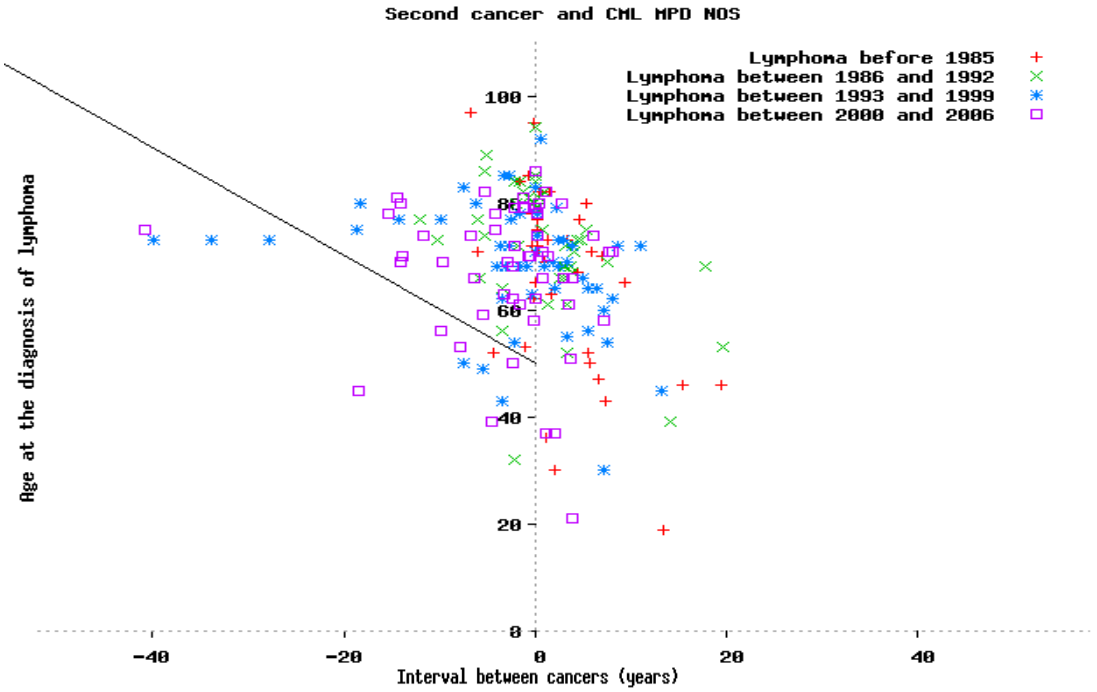


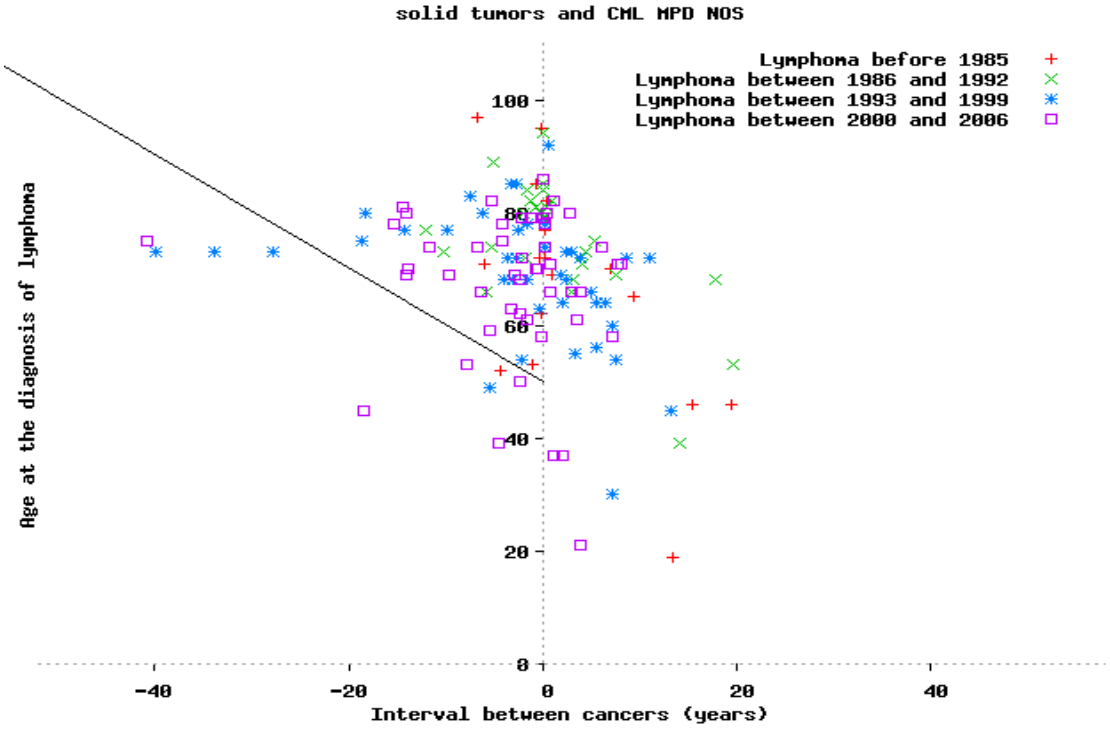
9.1.4 Associated cancers and Burkitt lymphoma, indeterminate NHL and non Burkitt NHL



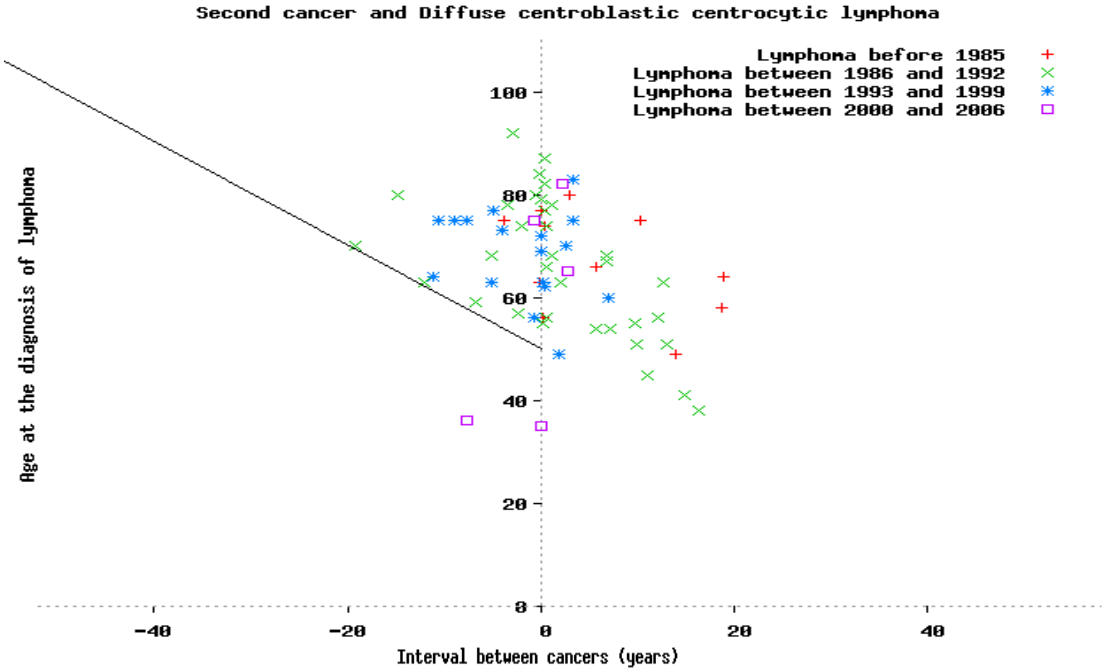


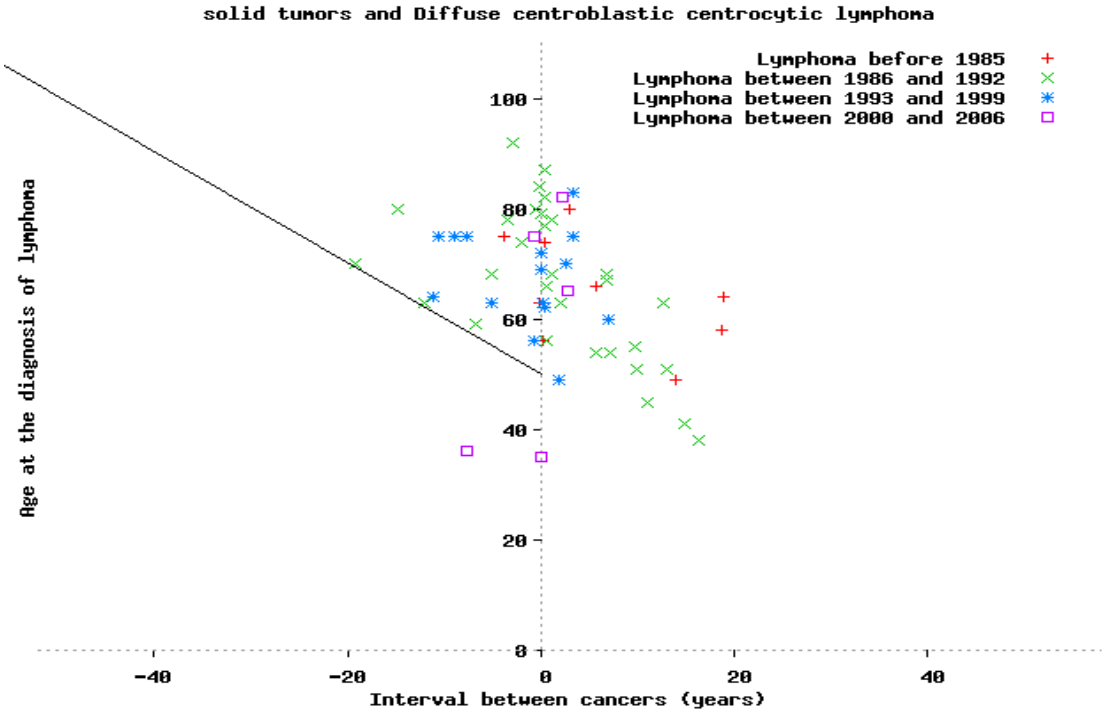
9.1.5 Associated cancers and CML and MPD NOS



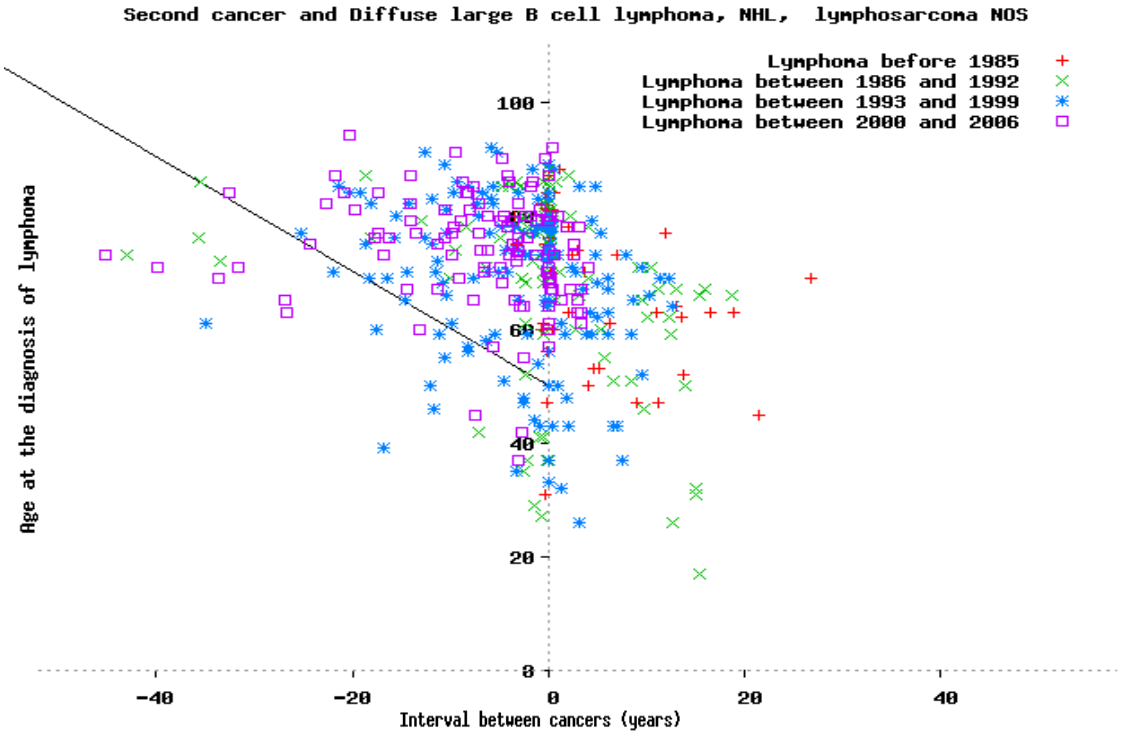


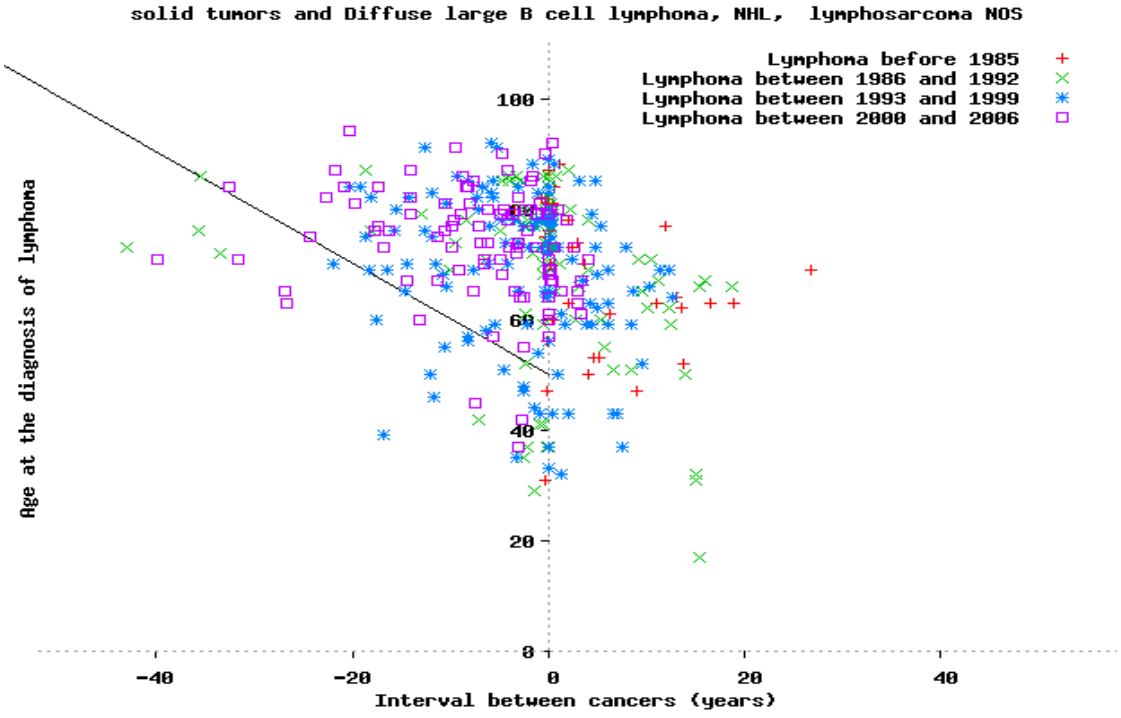
9.1.6 Associated cancers and diffuse centroblastic centrocytic lymphoma



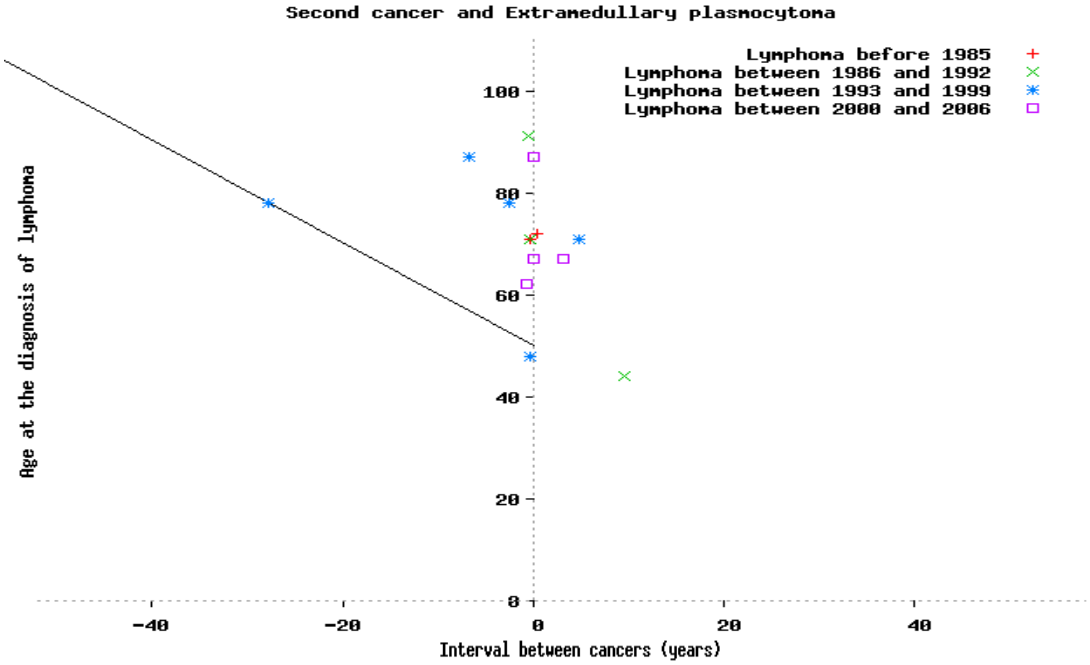


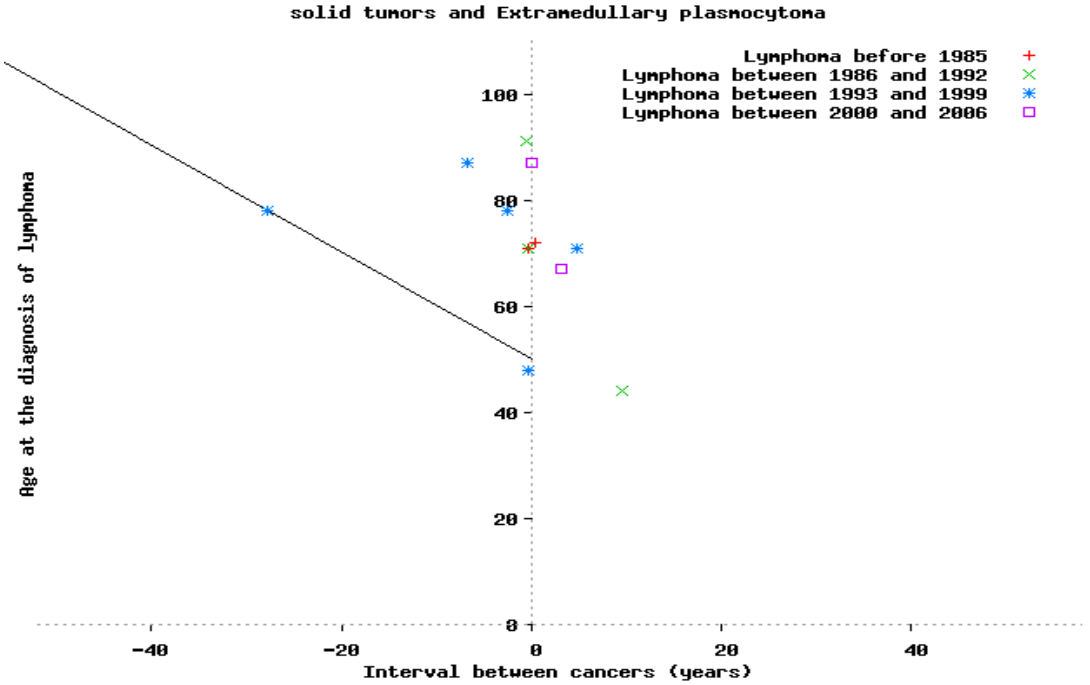
9.1.7 Associated cancers and DLBL



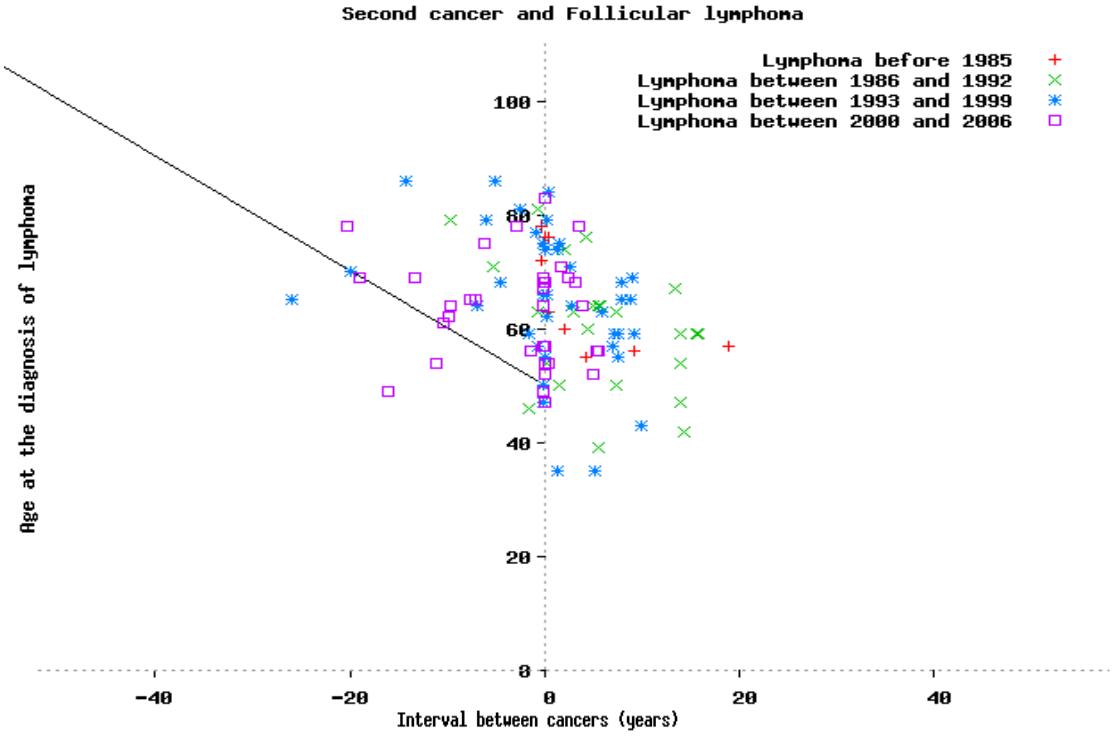


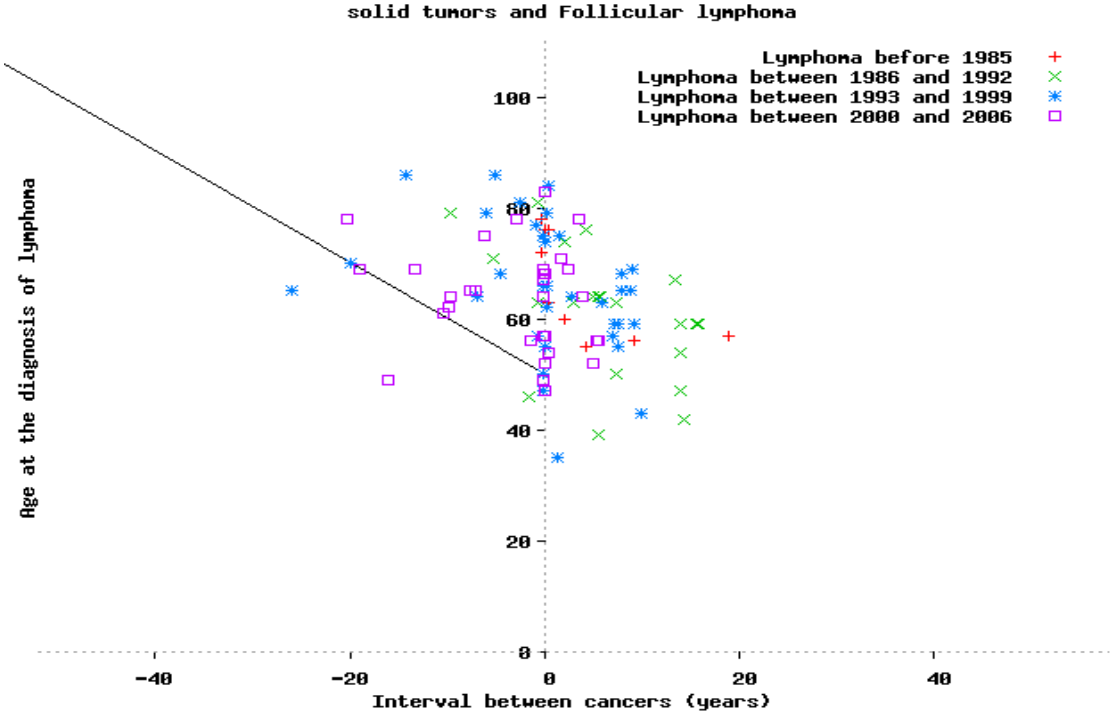
9.1.8 Associated cancers and extramedullary plasmocytoma



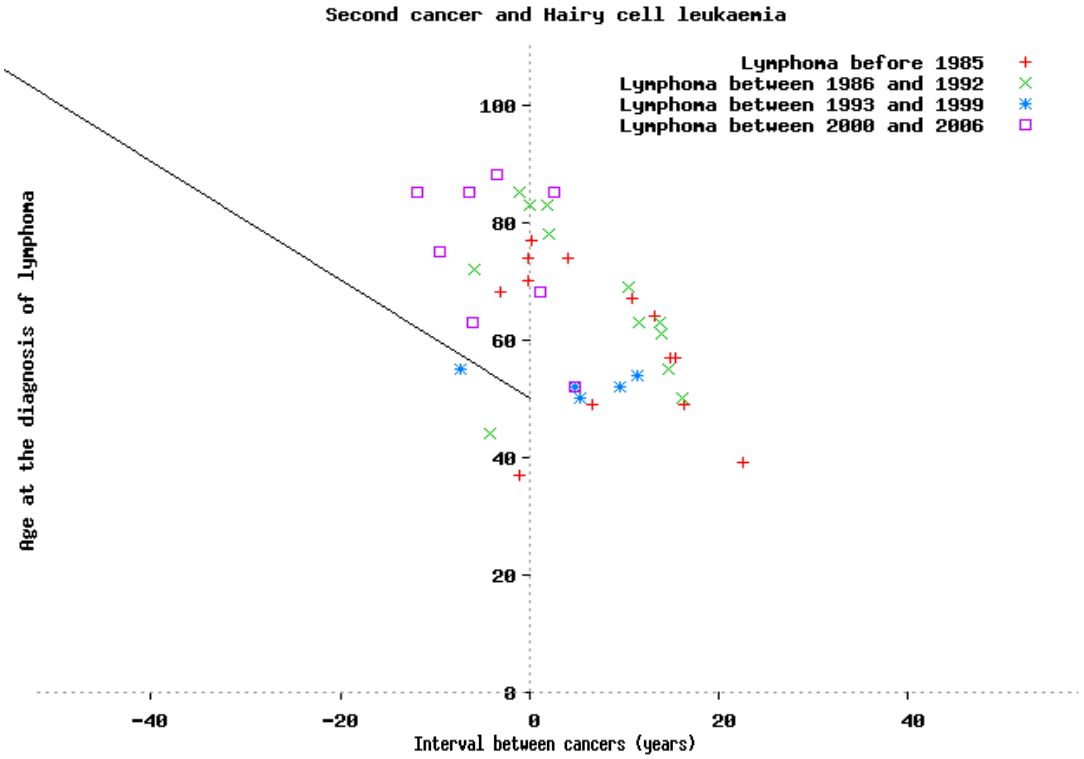


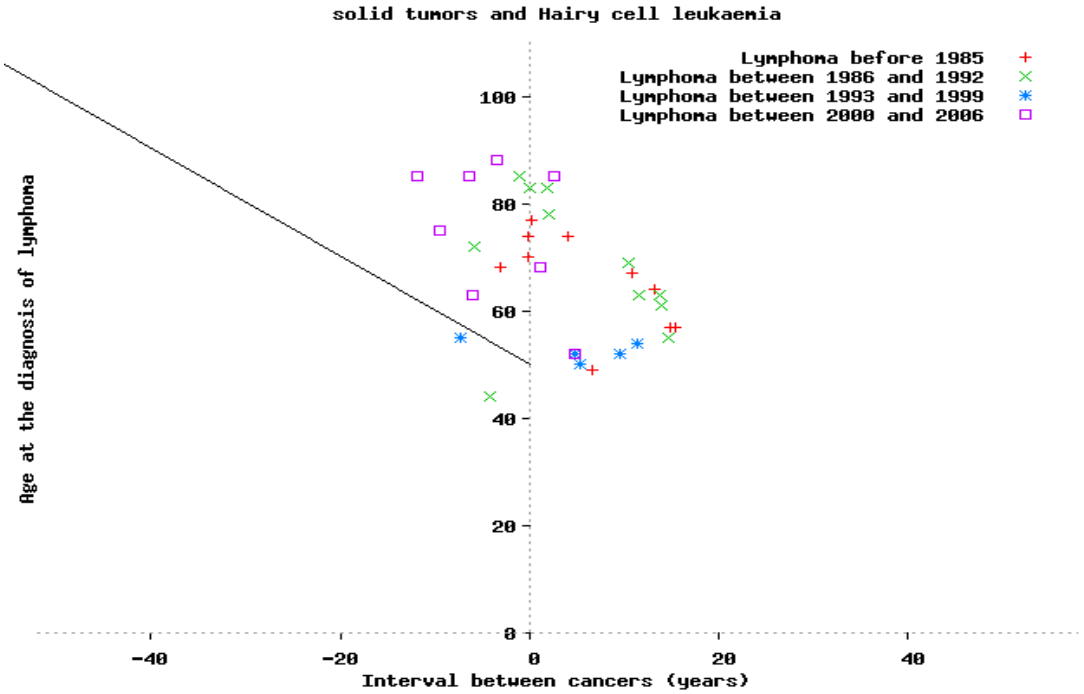
9.1.9 Associated cancers and FL



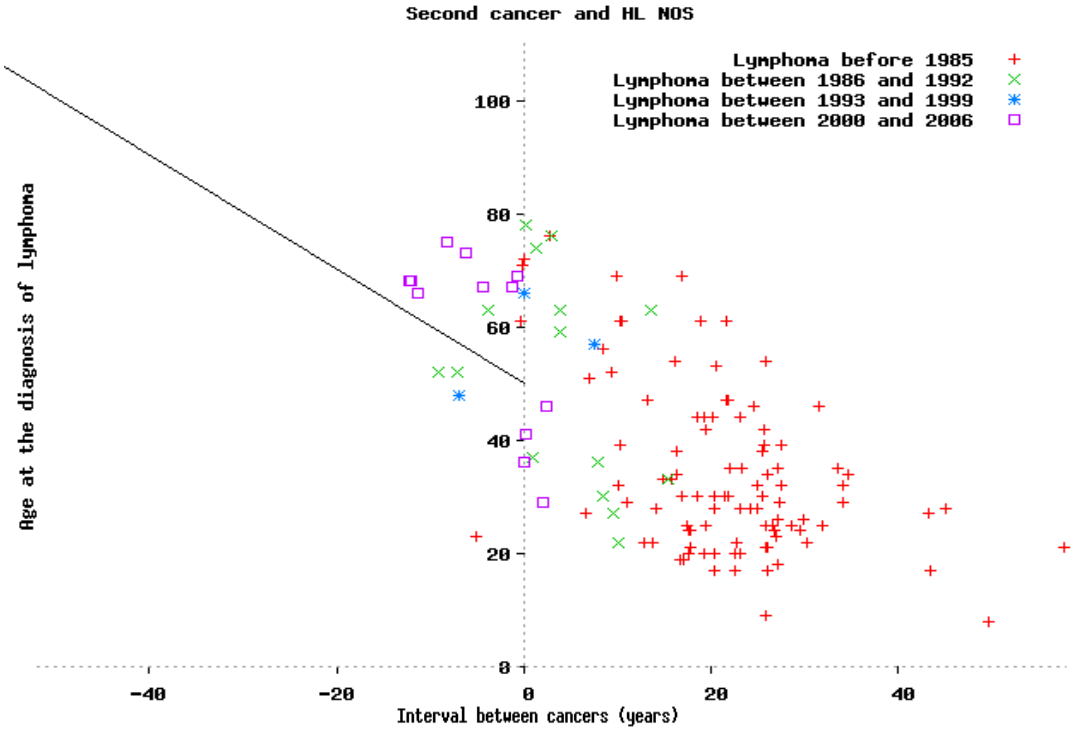


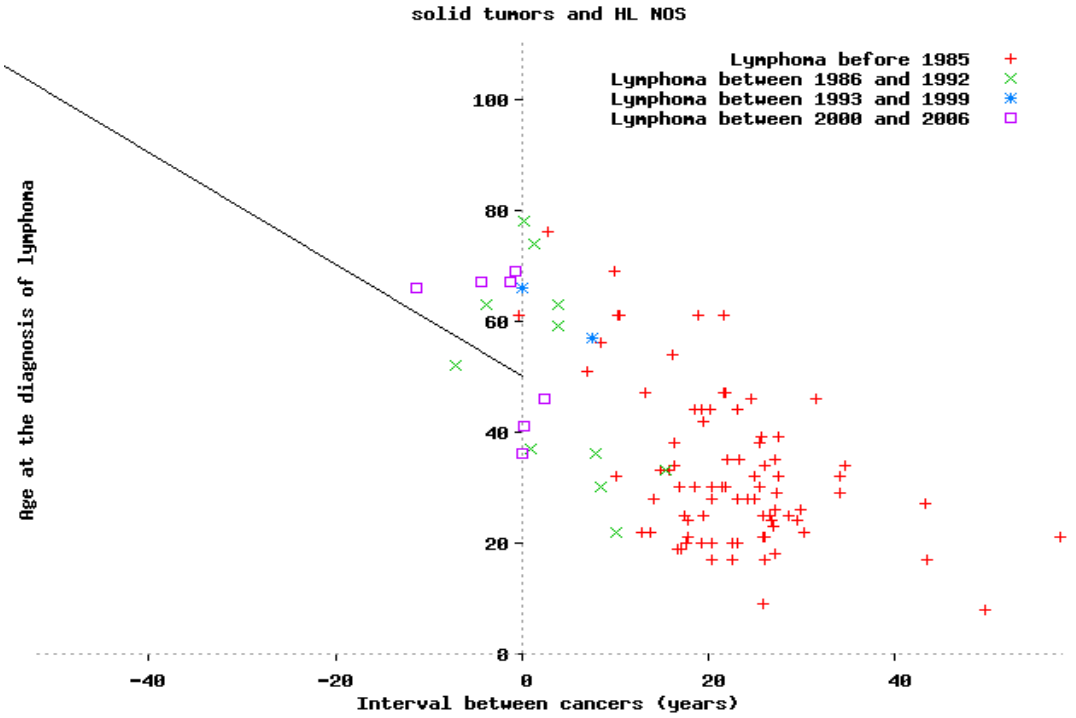
9.1.10 Associated cancers and HCL



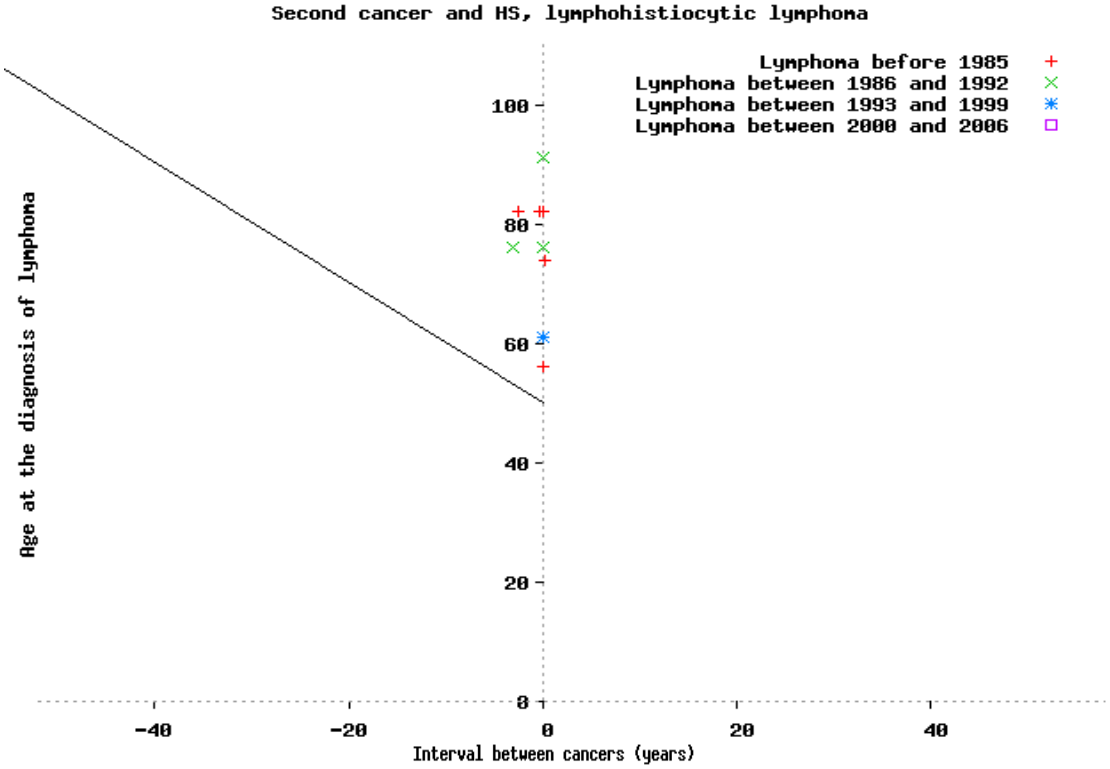


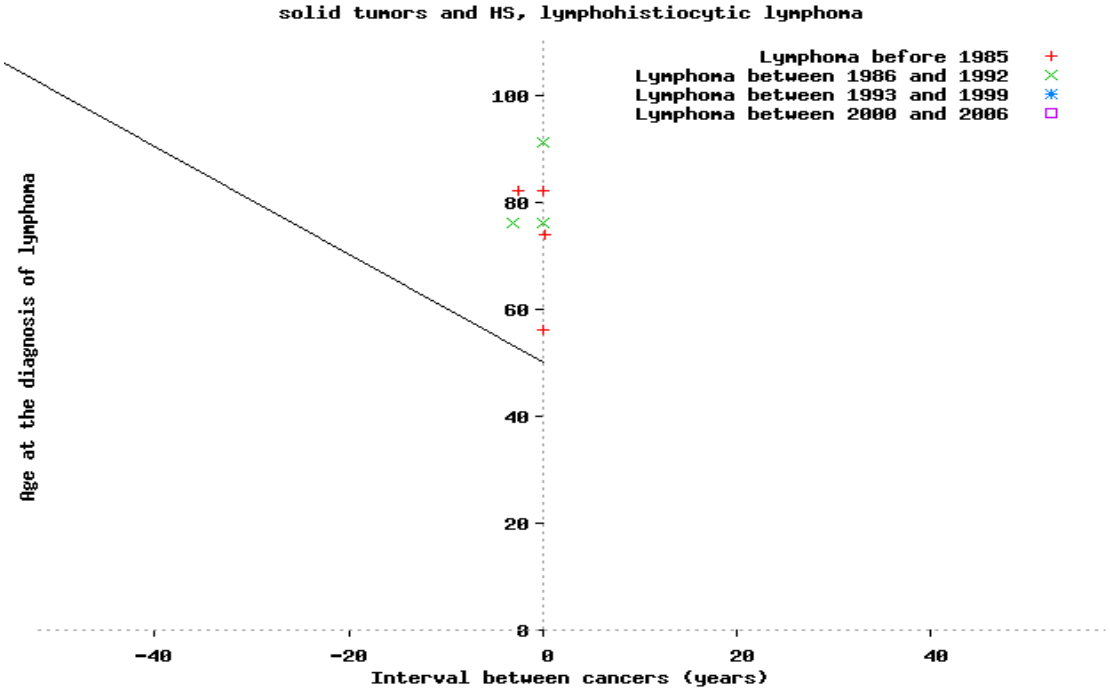
9.1.11 Associated cancers and HL NOS



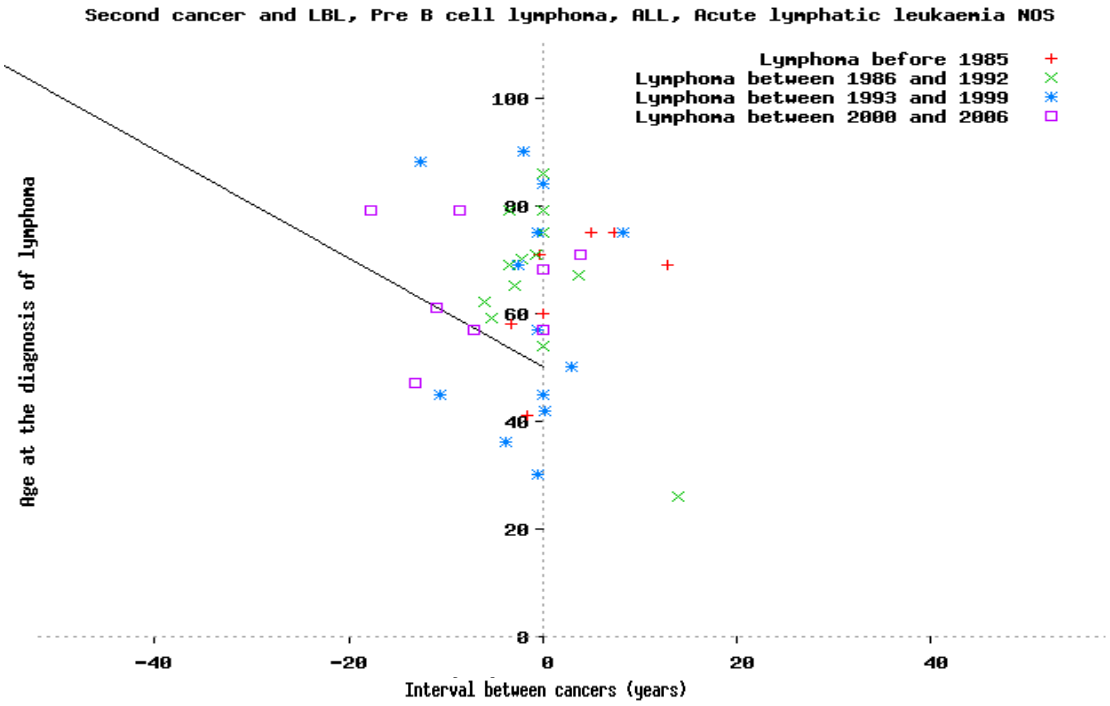


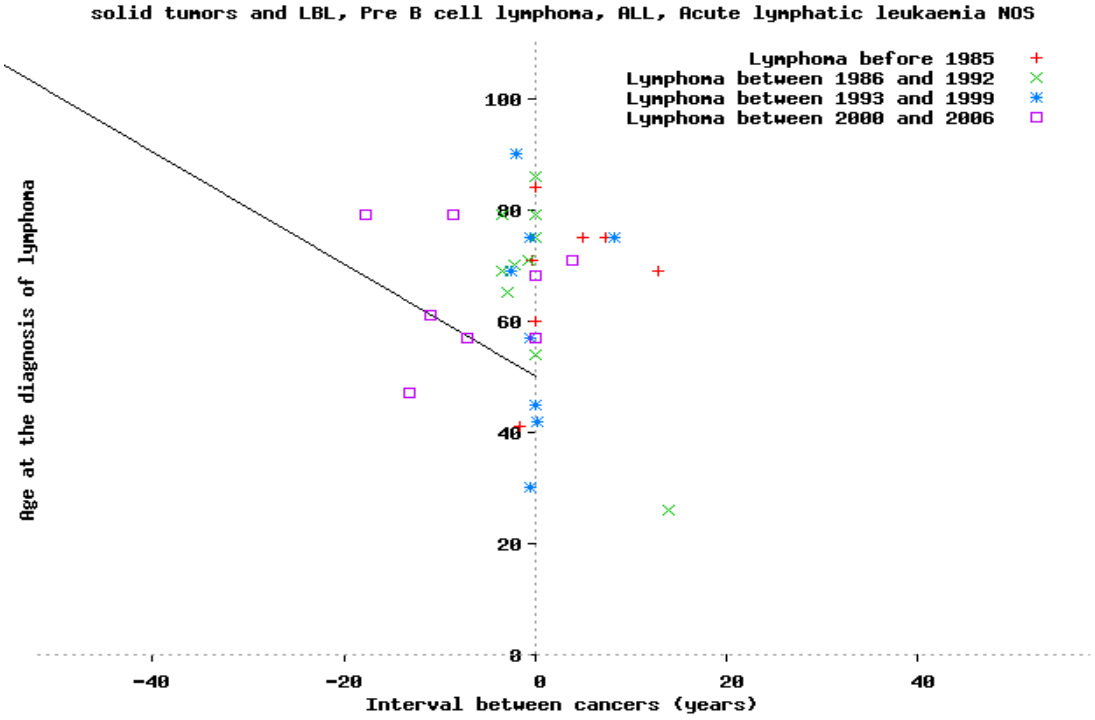
9.1.12 Associated cancers and histiocytic lymphoma



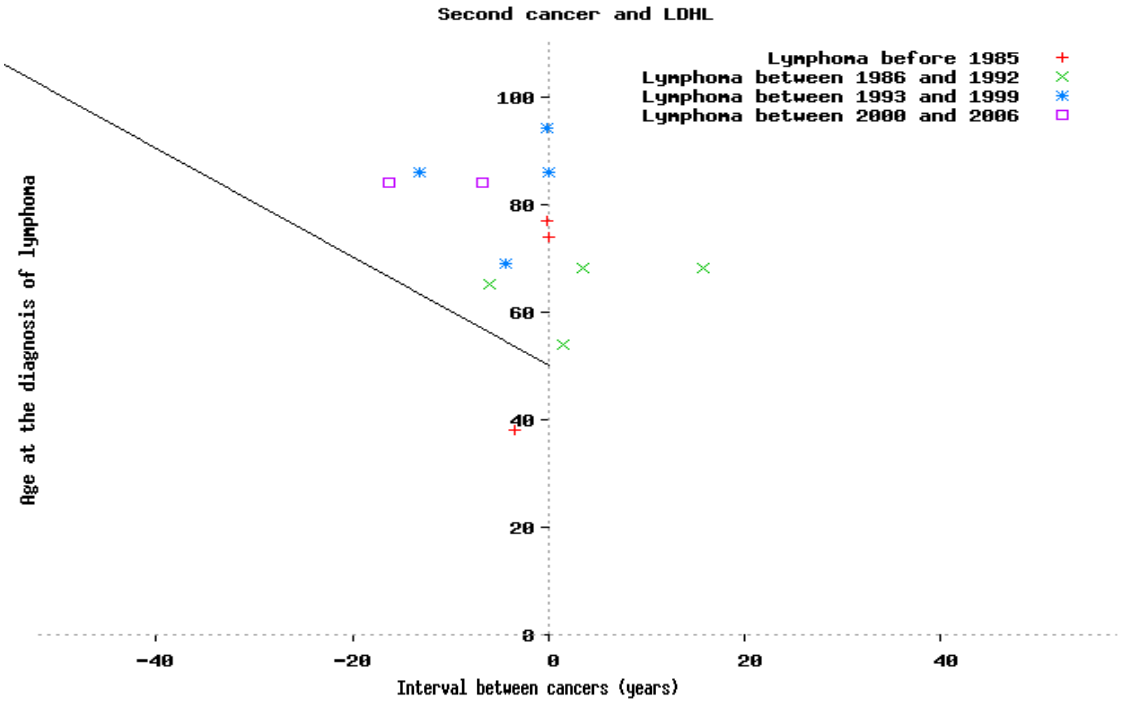


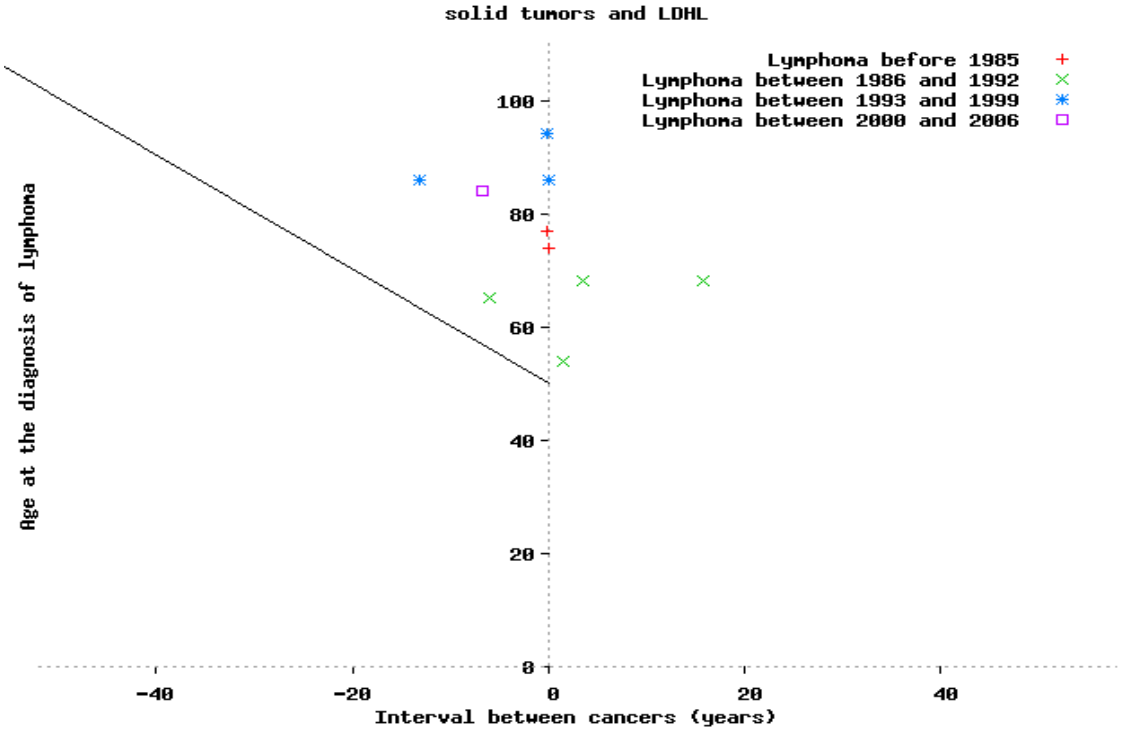
9.1.13 Associated cancers and ALL



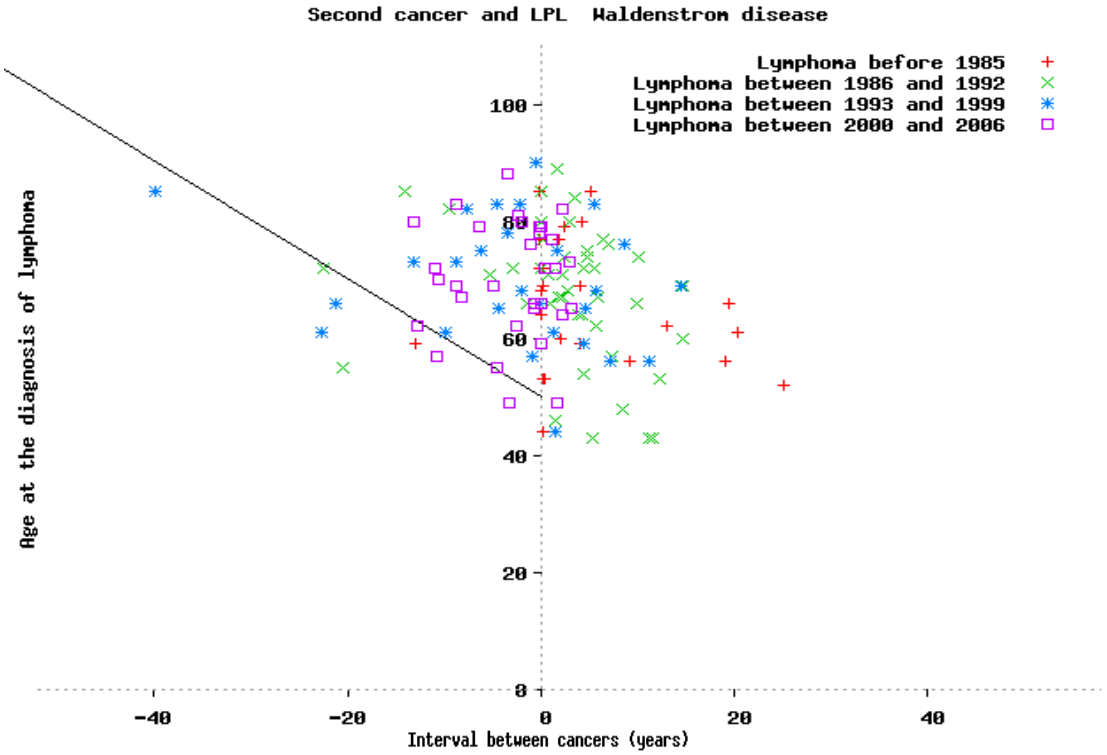


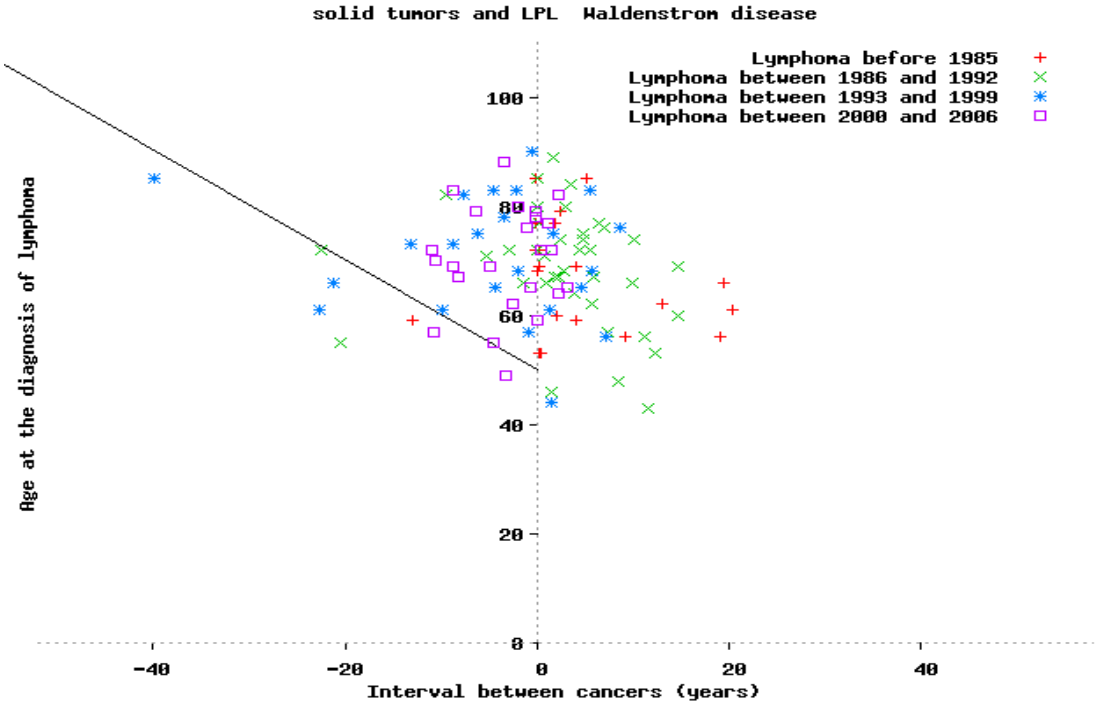
9.1.14 Associated cancers and LDHL



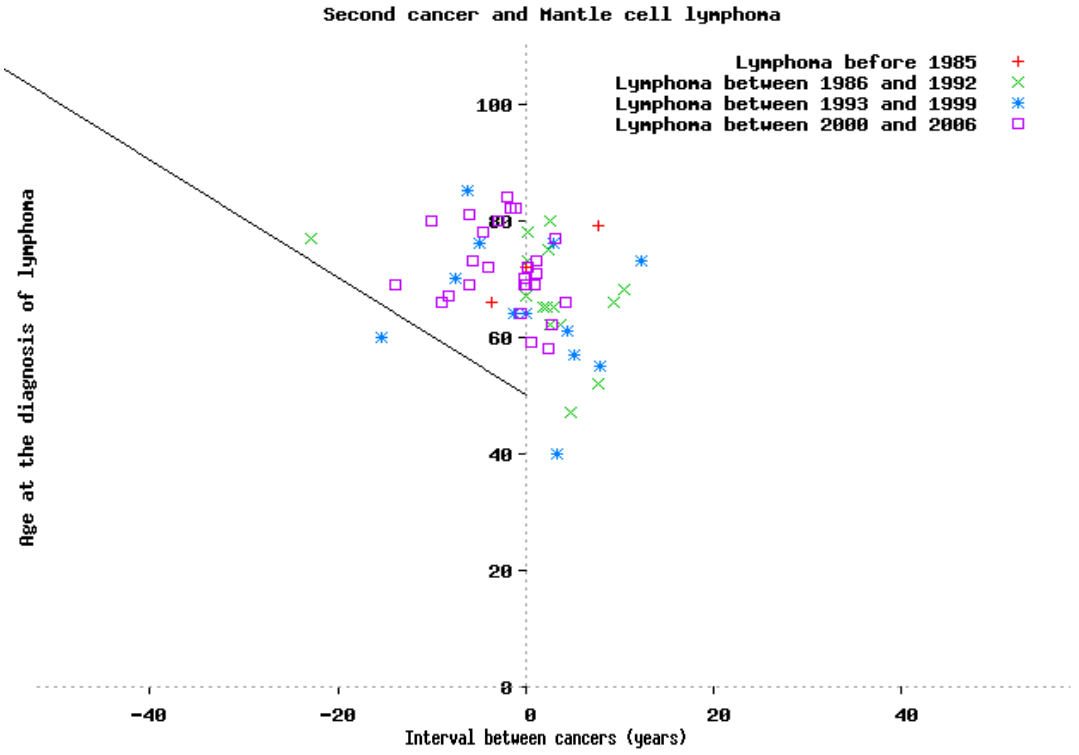


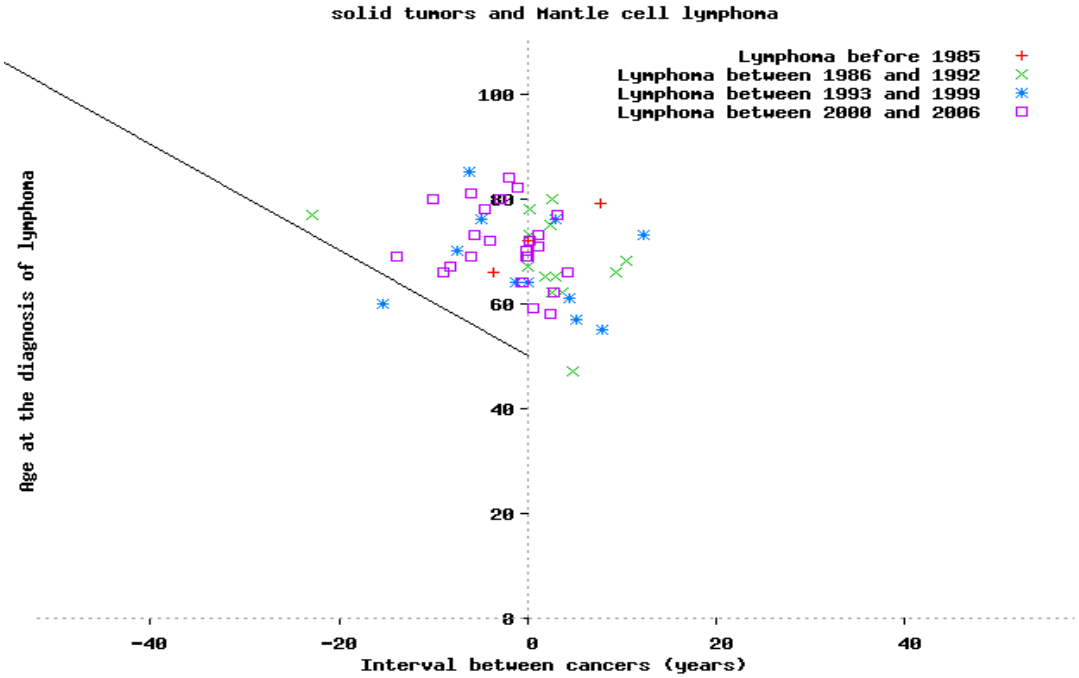
9.1.15 Associated cancers and LPL



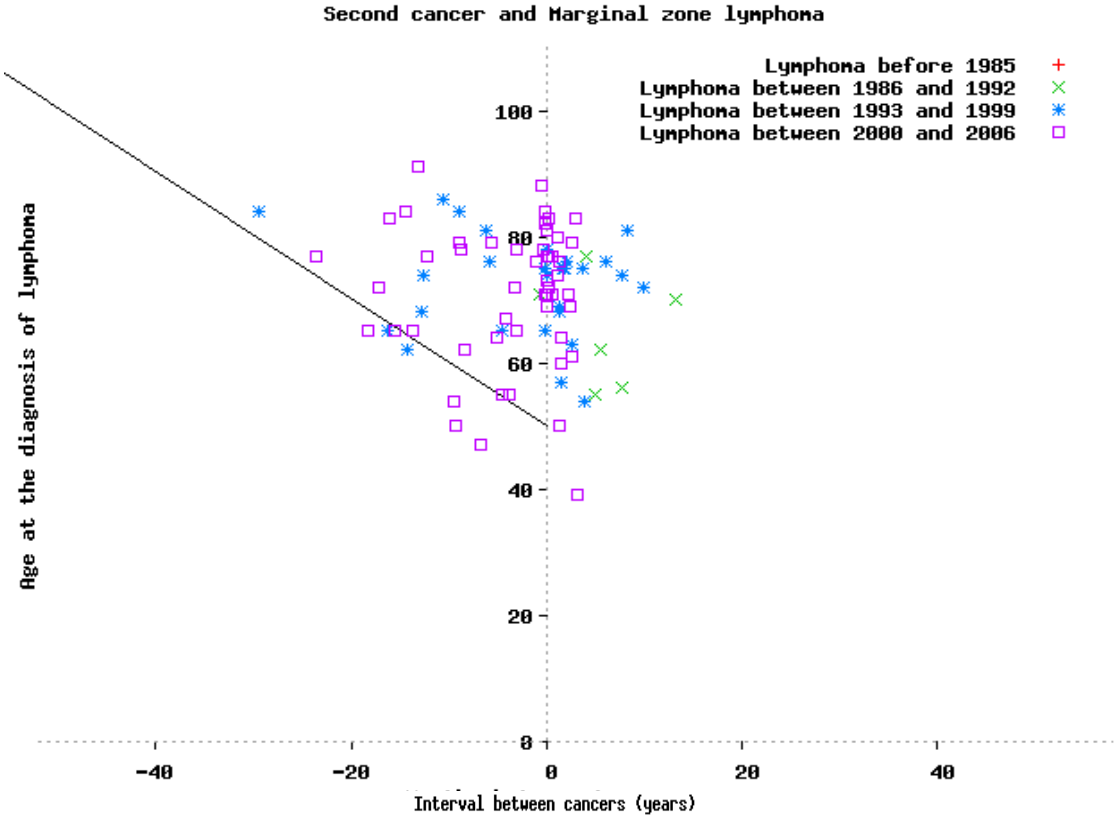


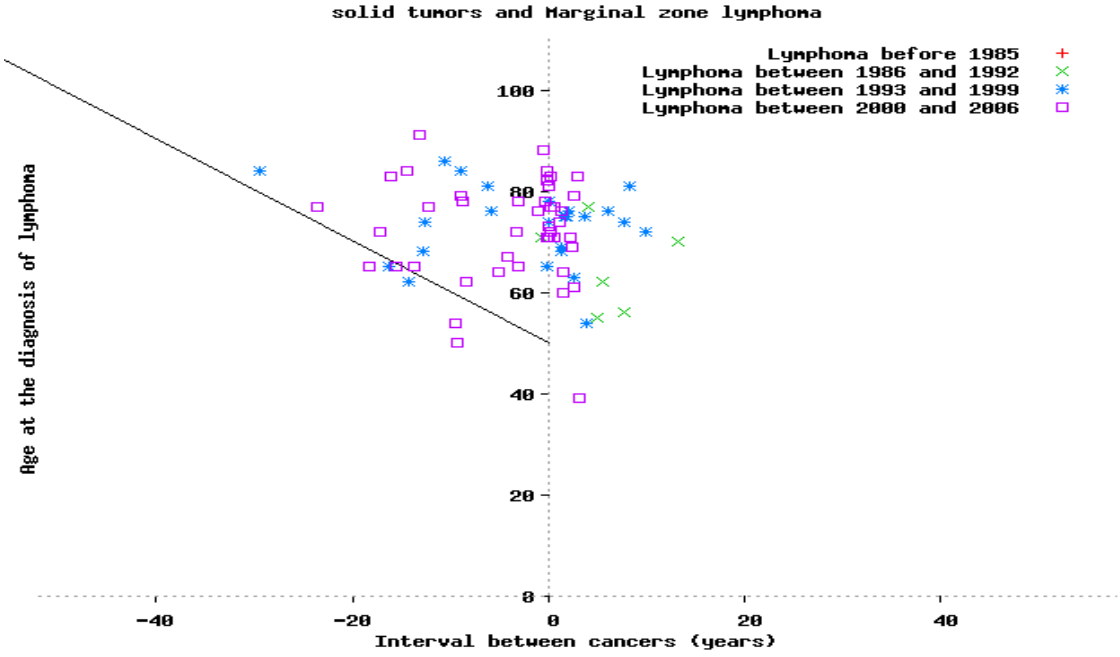
9.1.16 Associated cancers and MCL



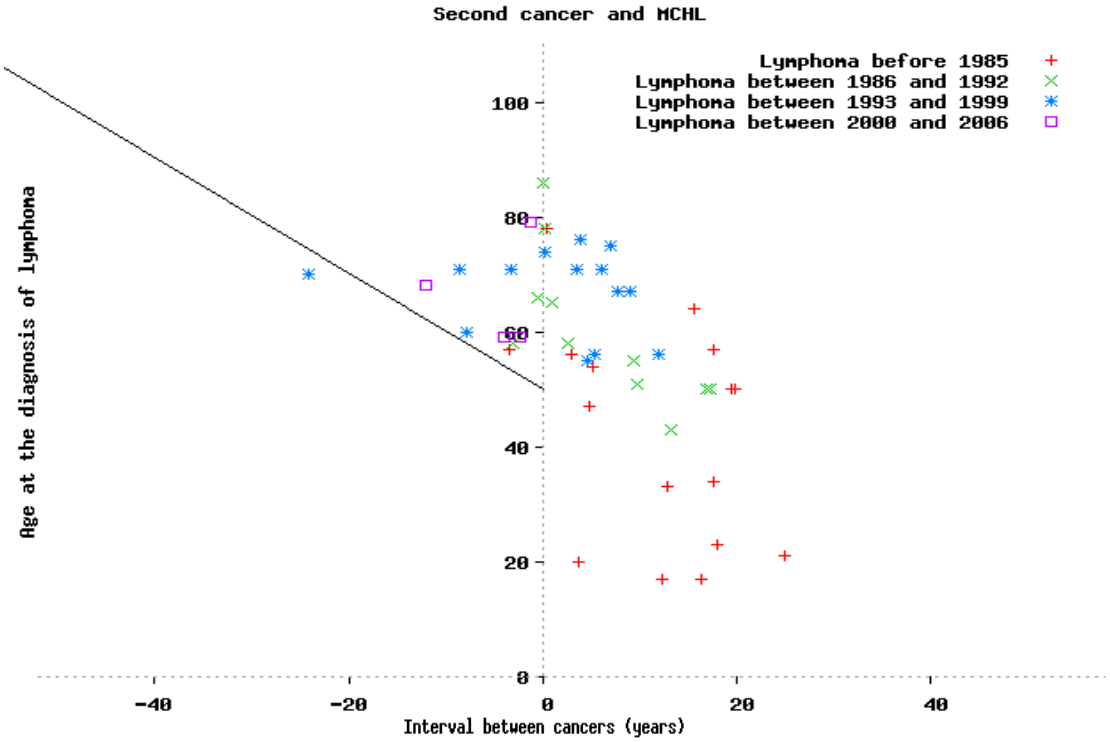


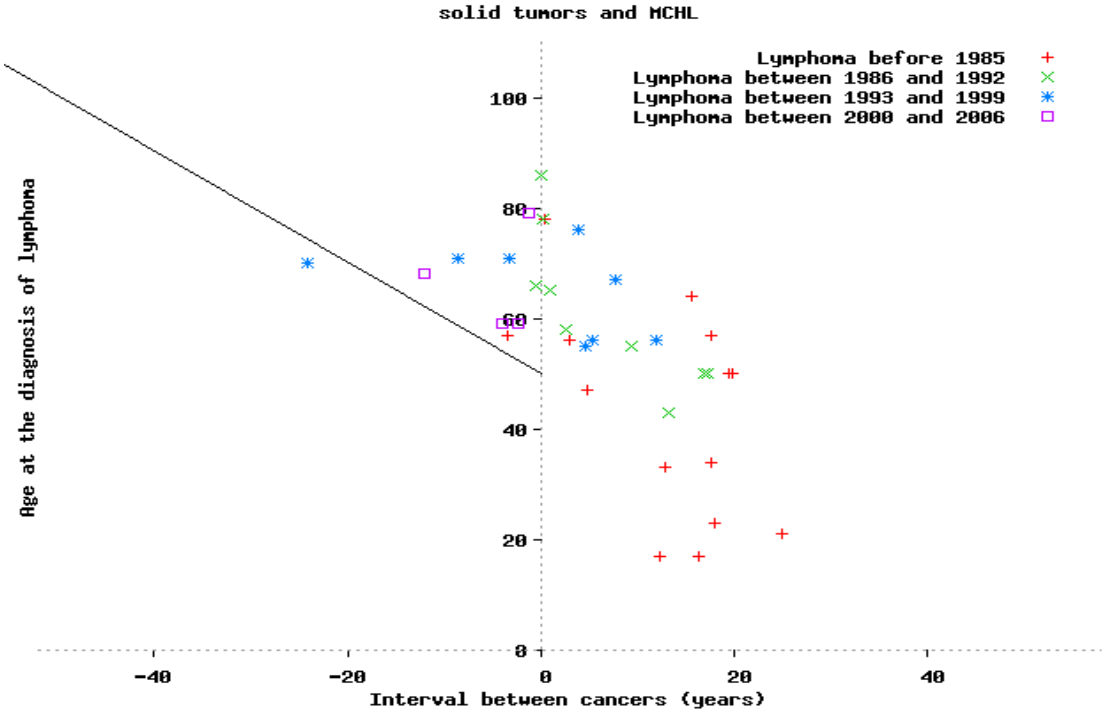
9.1.17 Associated cancers and marginal zone lymphoma



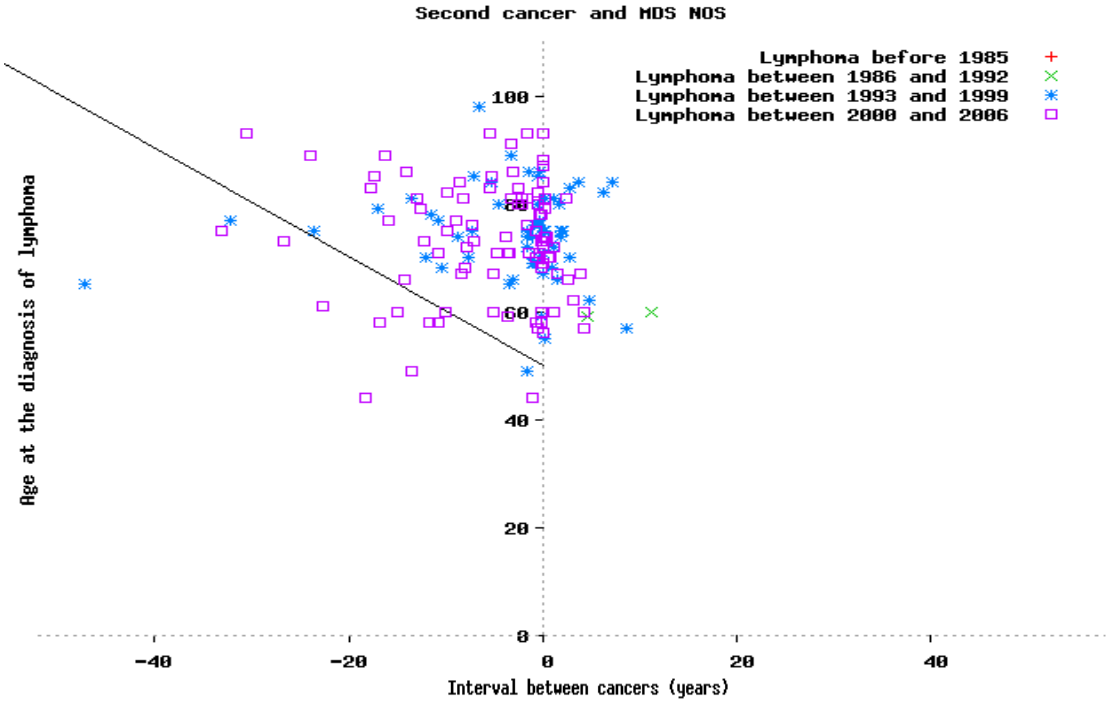


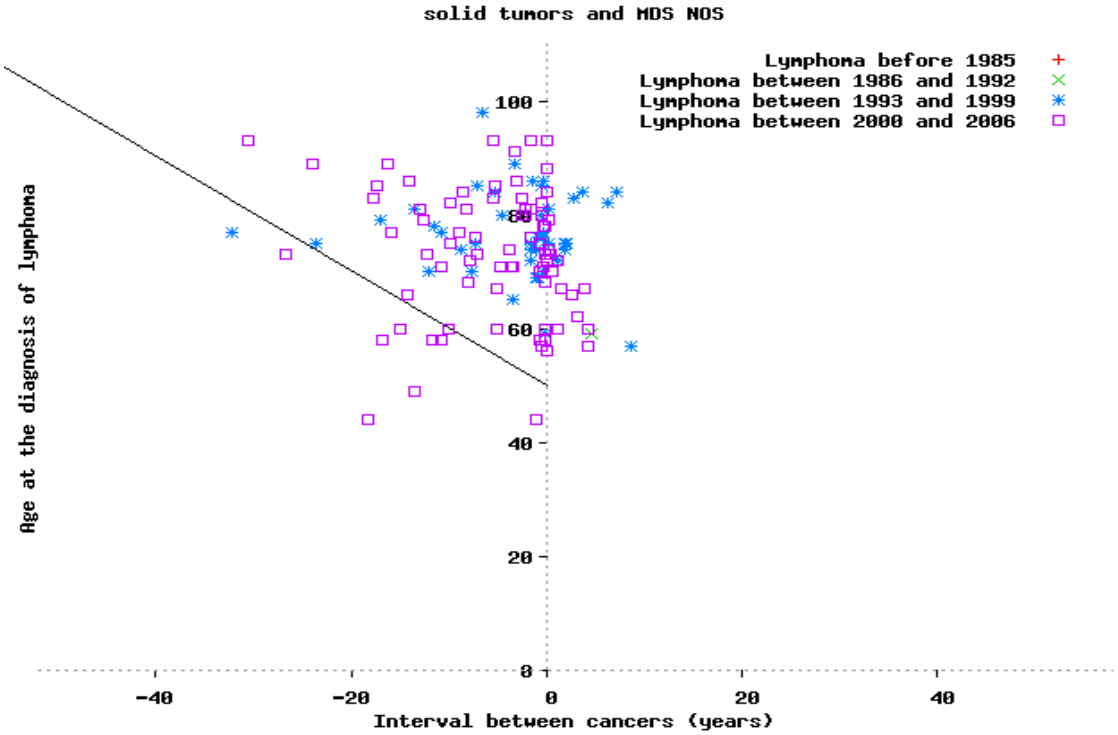
9.1.18 Associated cancers and MCHL



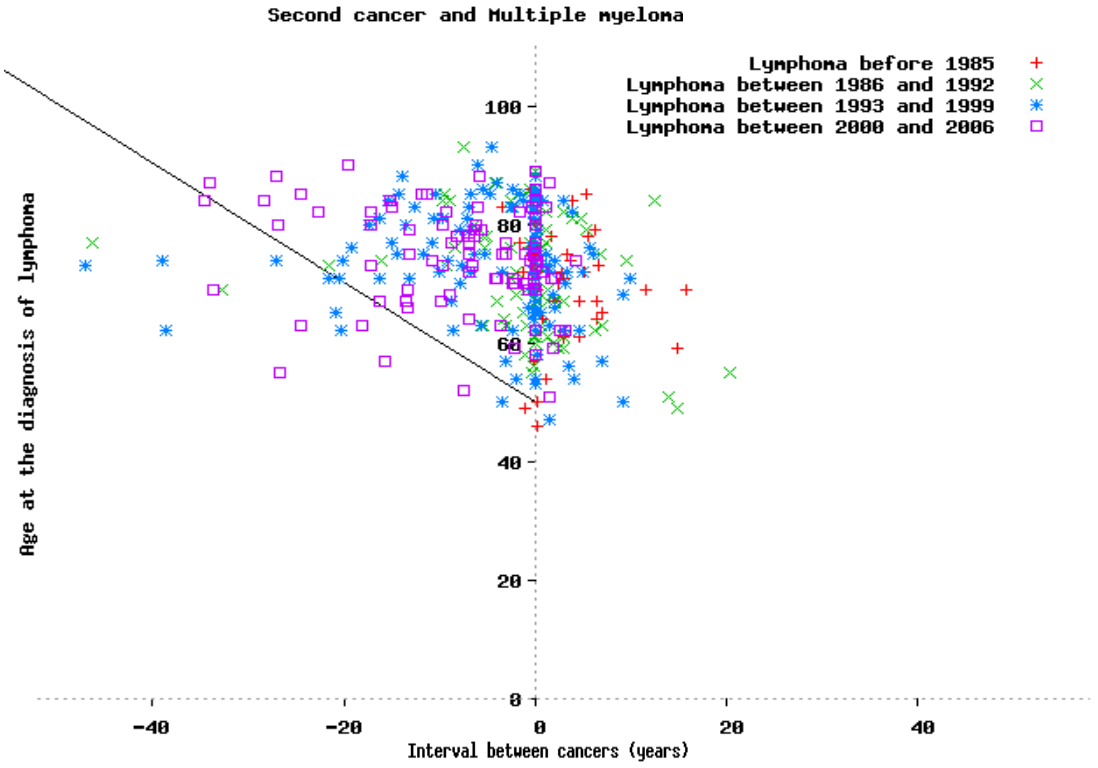


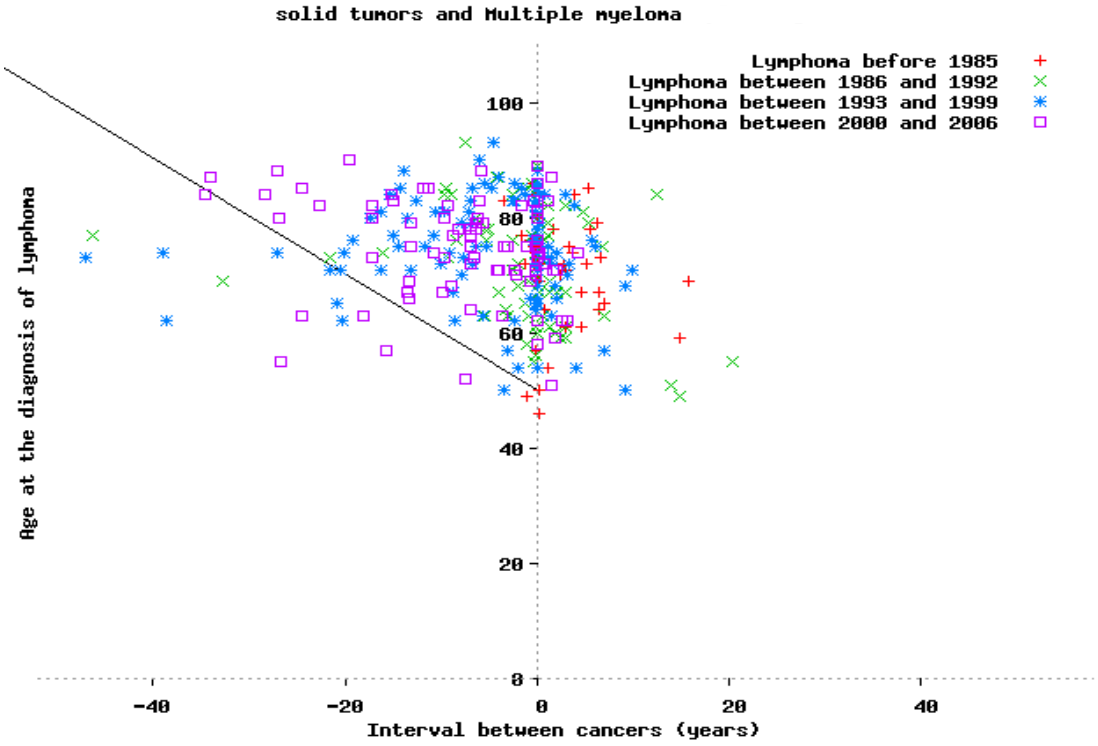
9.1.19 Associated cancers and MDS



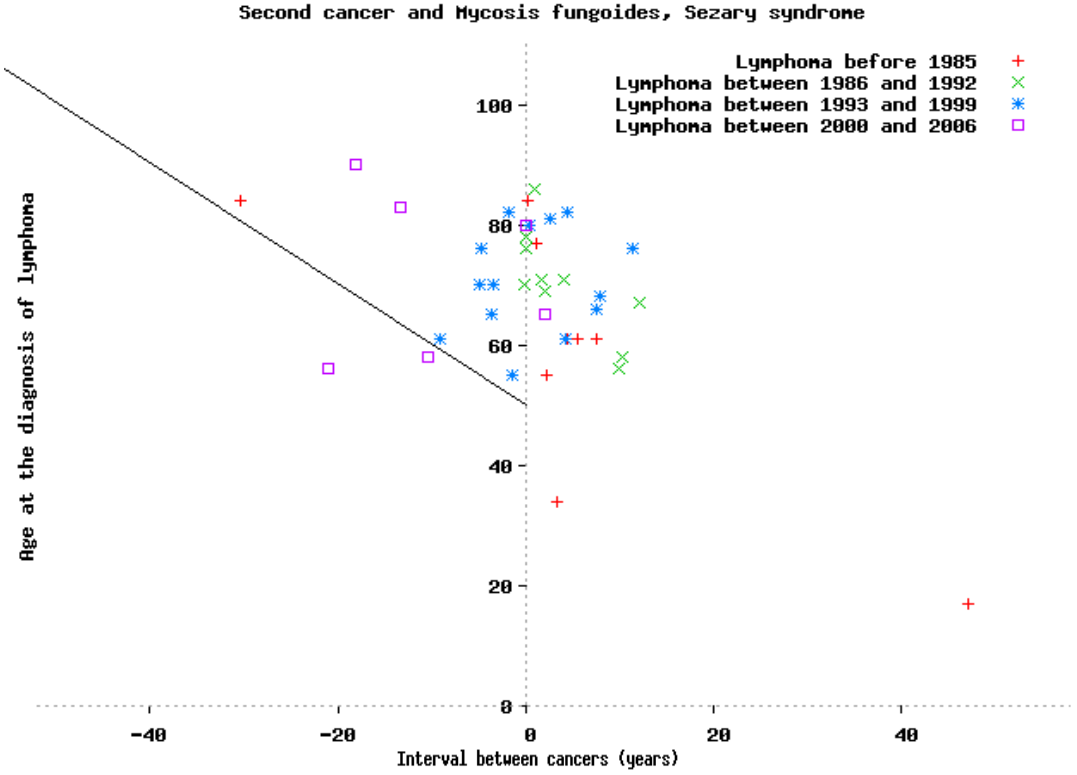


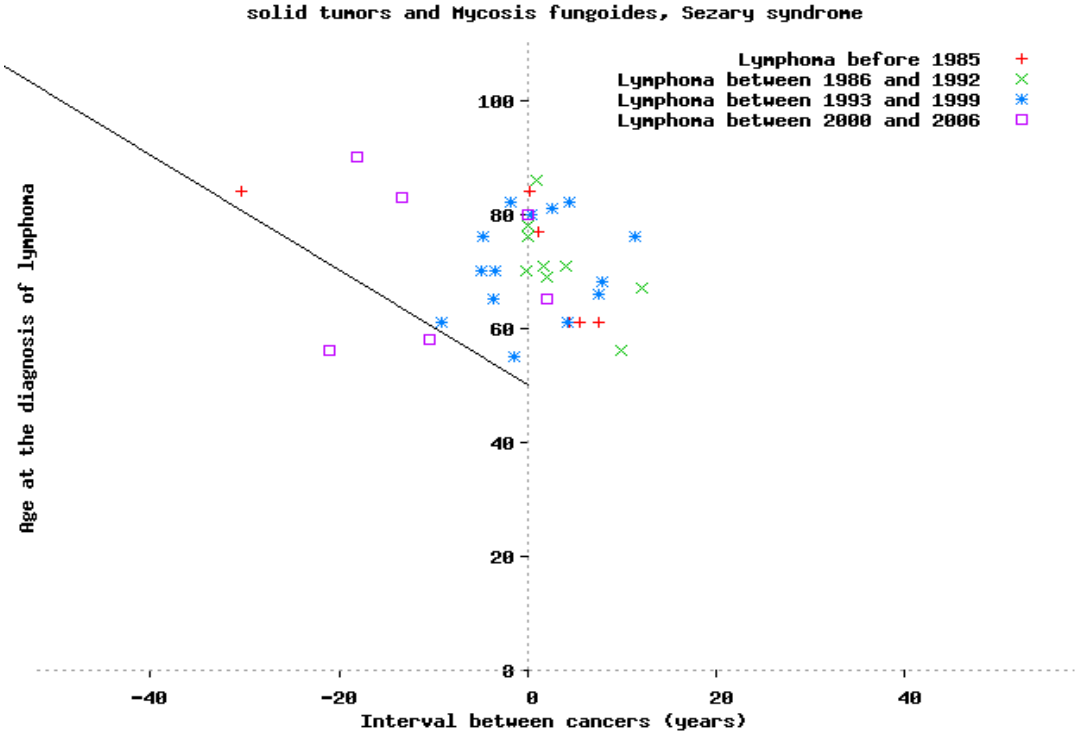
9.1.20 Associated cancers and MM



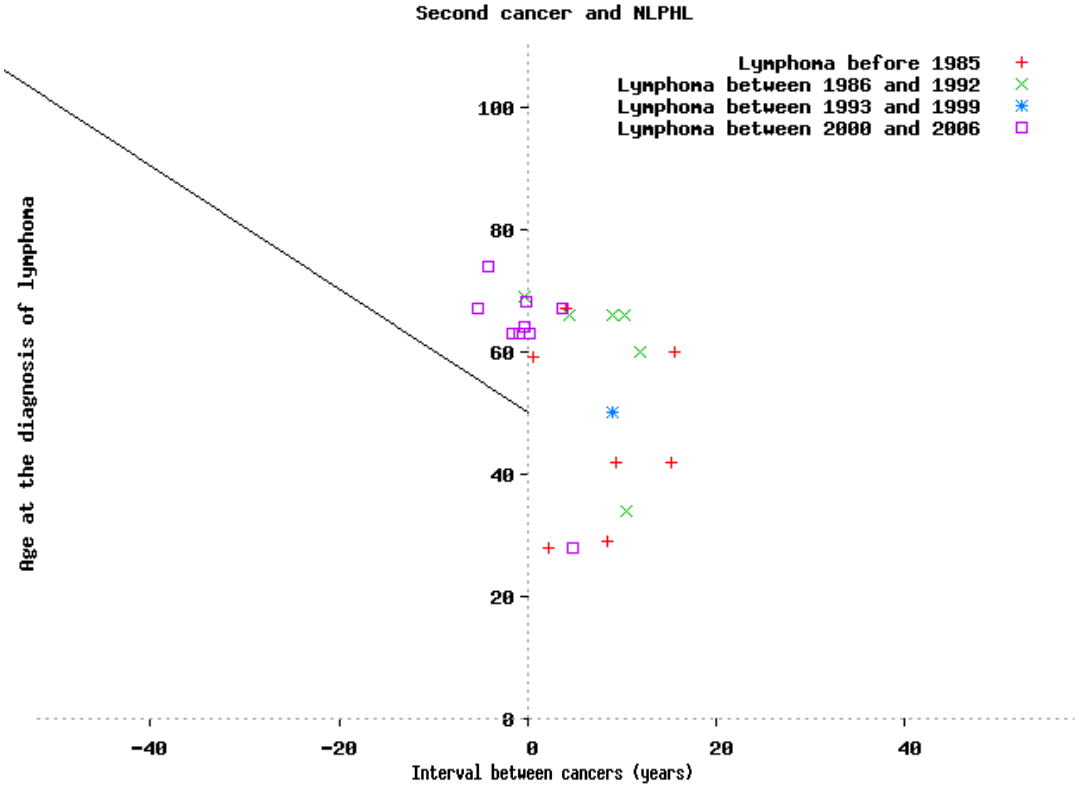


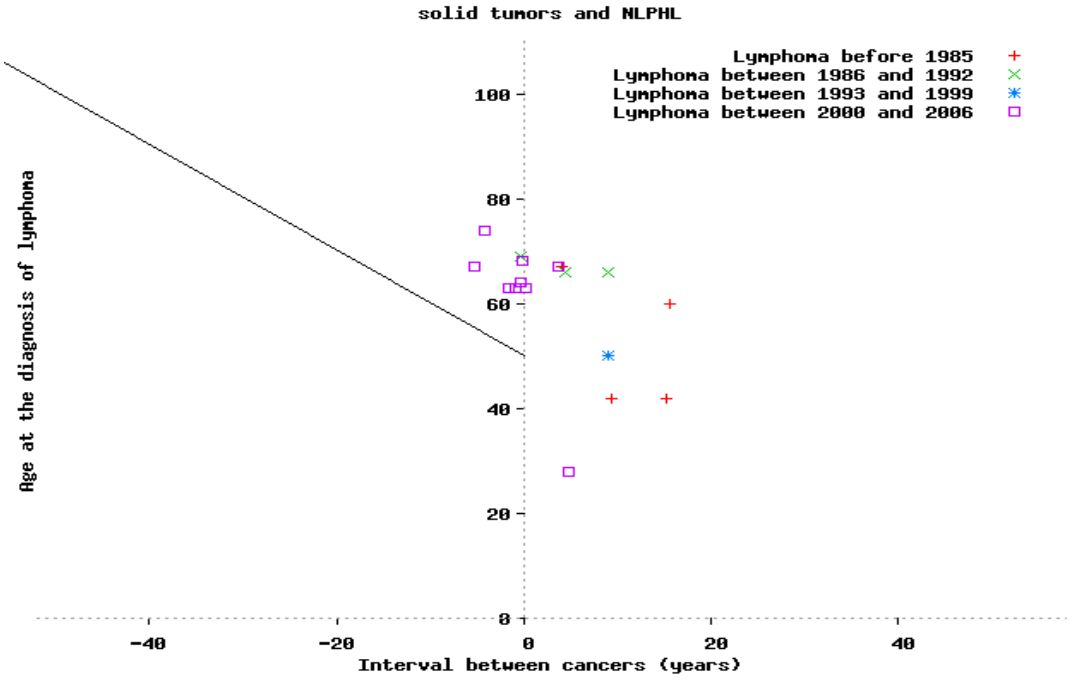
9.1.21 Associated cancers and Mycosis fungoides including Sezary syndrome



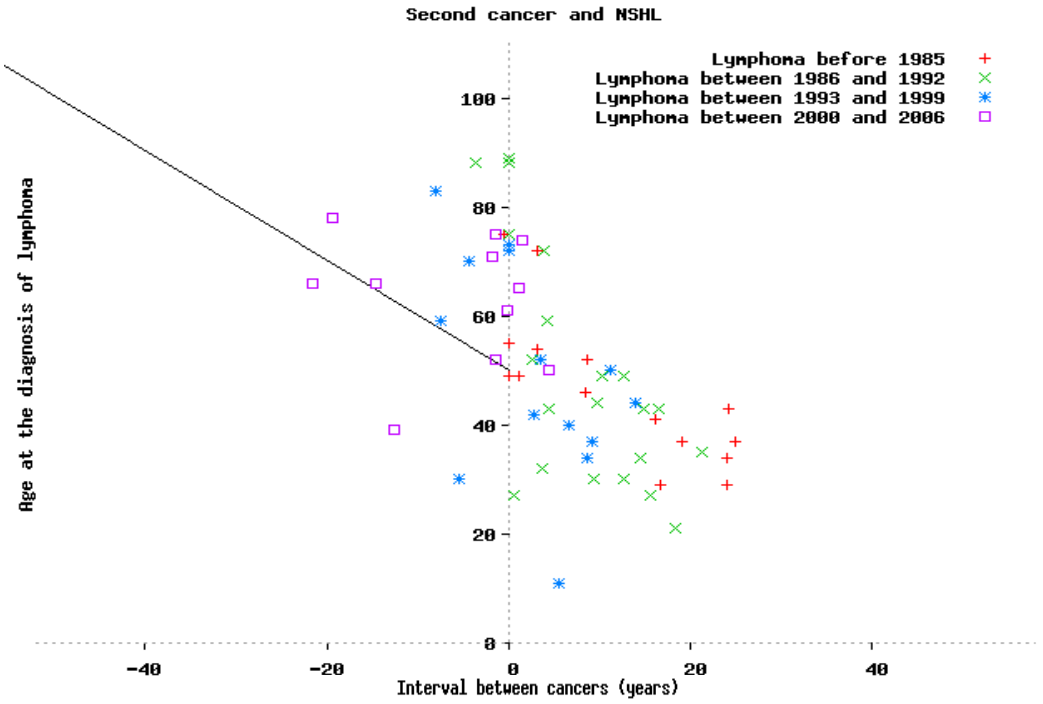


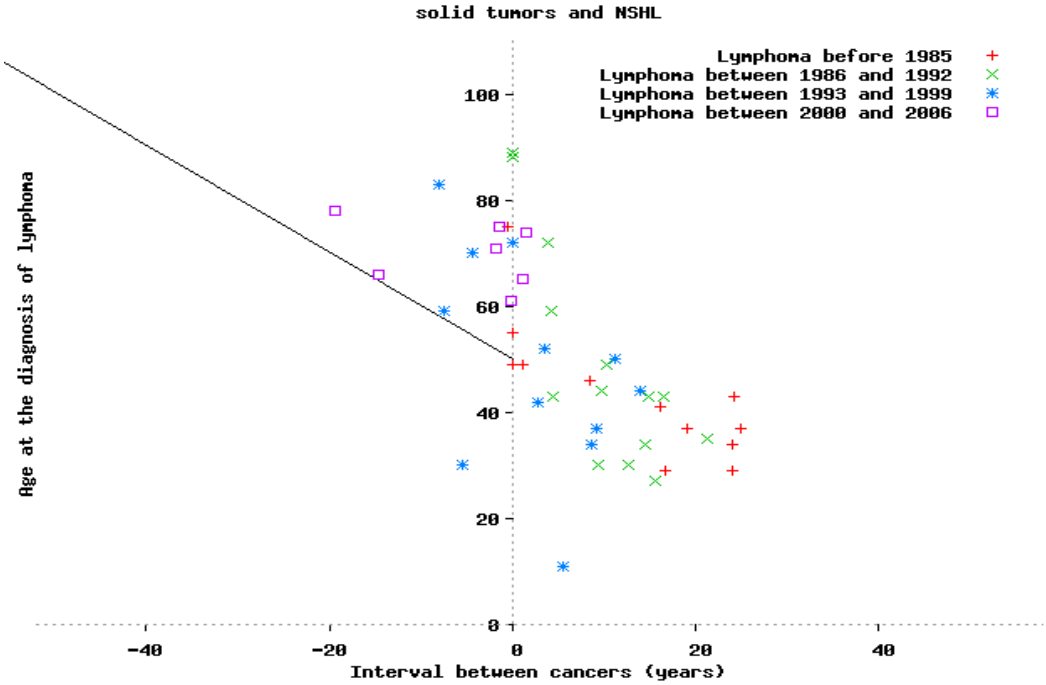
9.1.22 Associated cancers and NLPHL



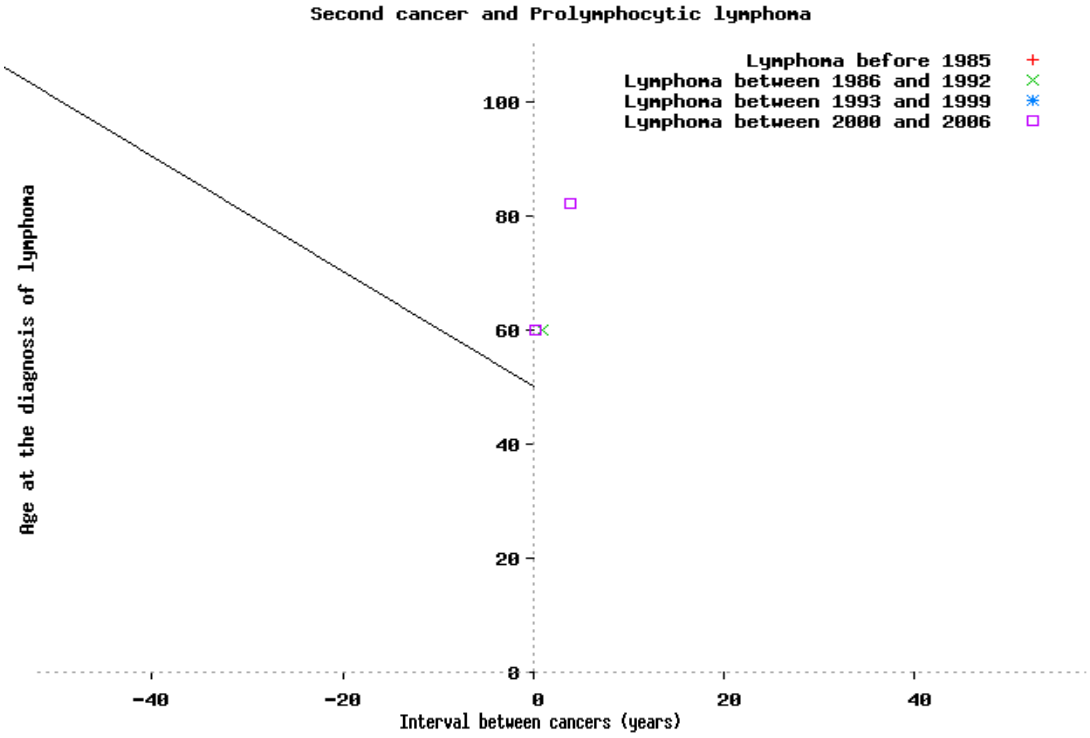


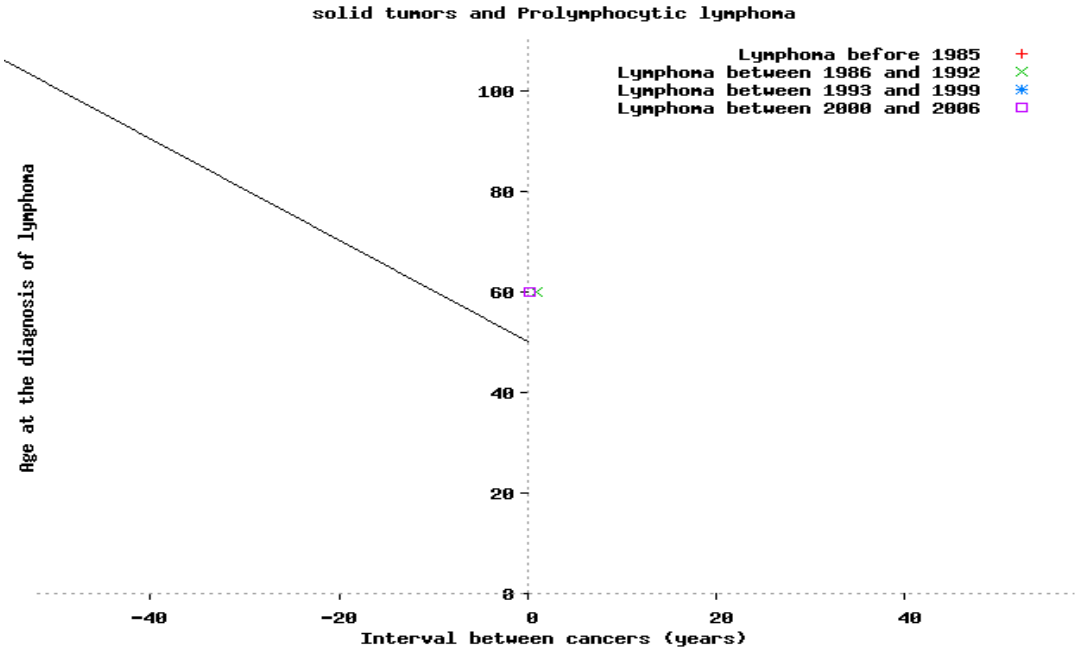
9.1.23 Associated cancers and NSHL



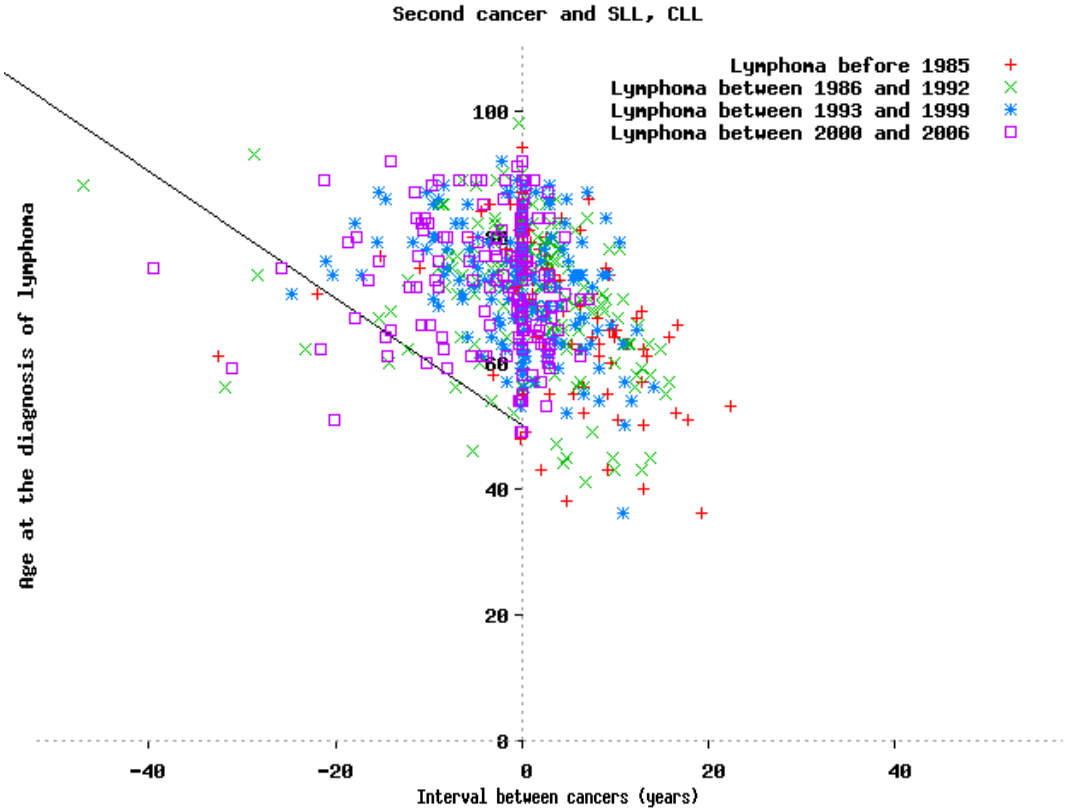


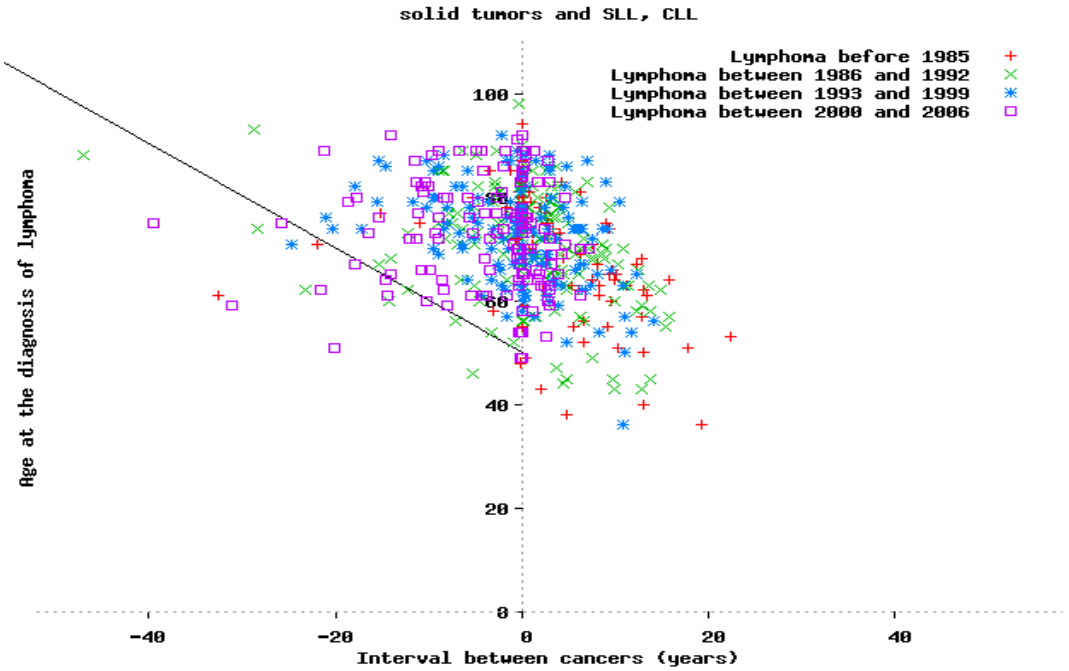
9.1.24 Associated cancers and prolymphocytic lymphoma



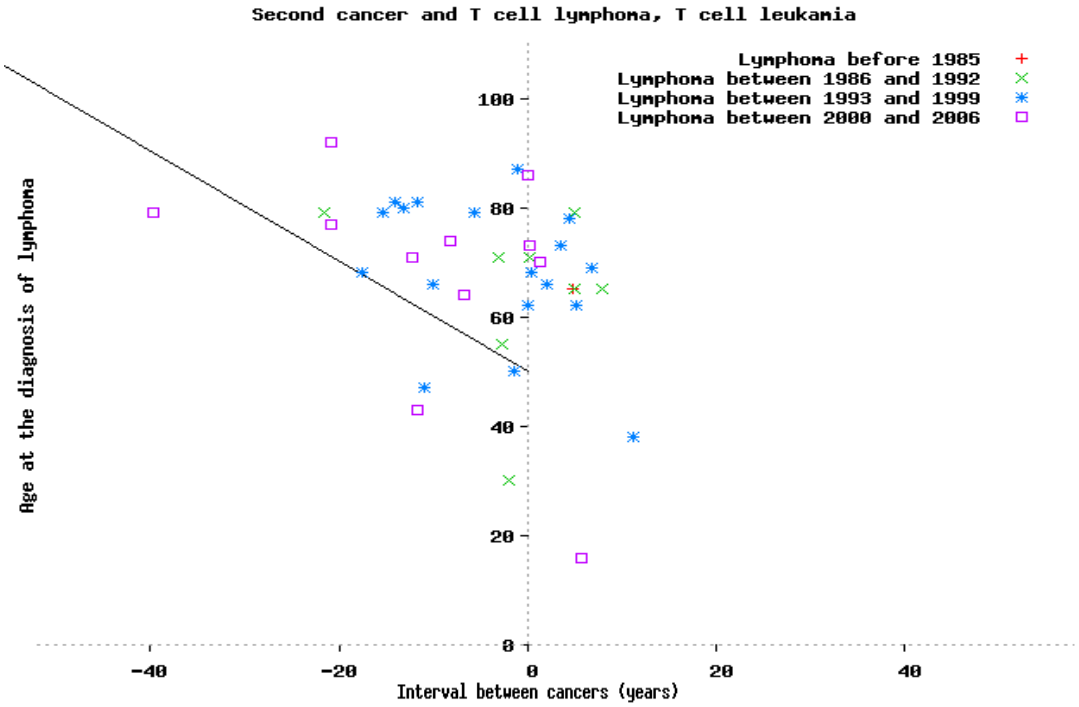


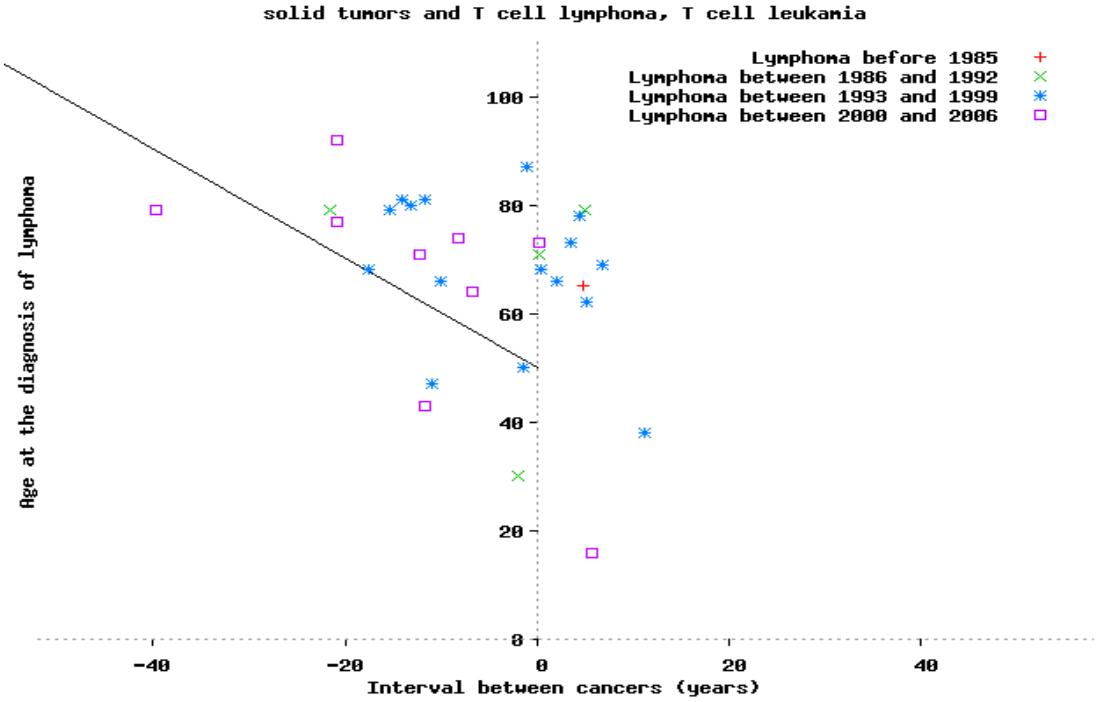
9.1.25 Associated cancers and SLL-CLL





9.1.26 Associated cancers and T cell lymphoma



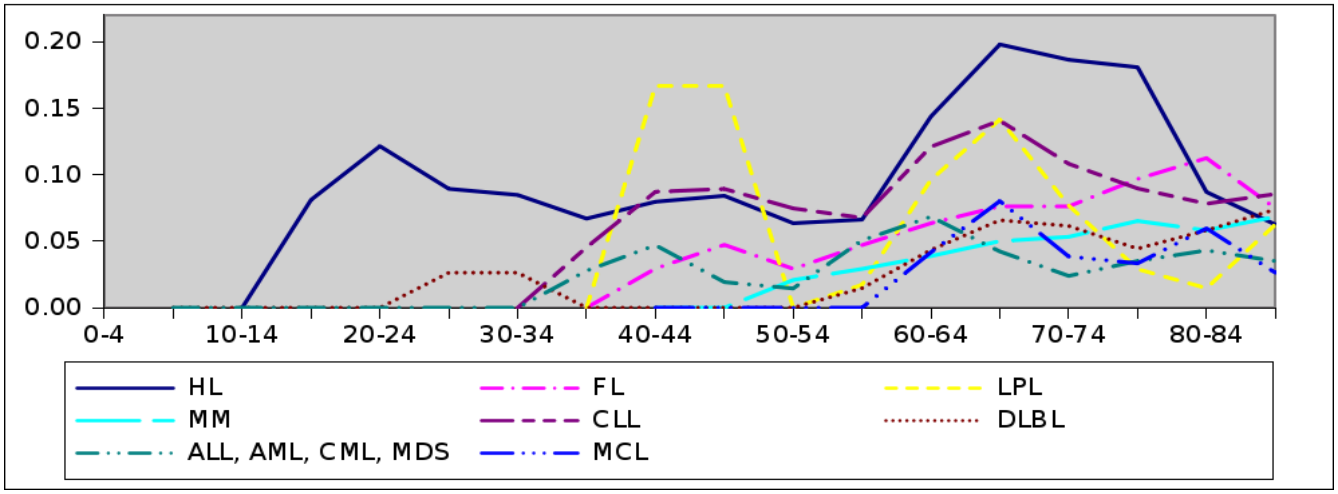


9.2 Incidence rates of associated malignant neoplasms

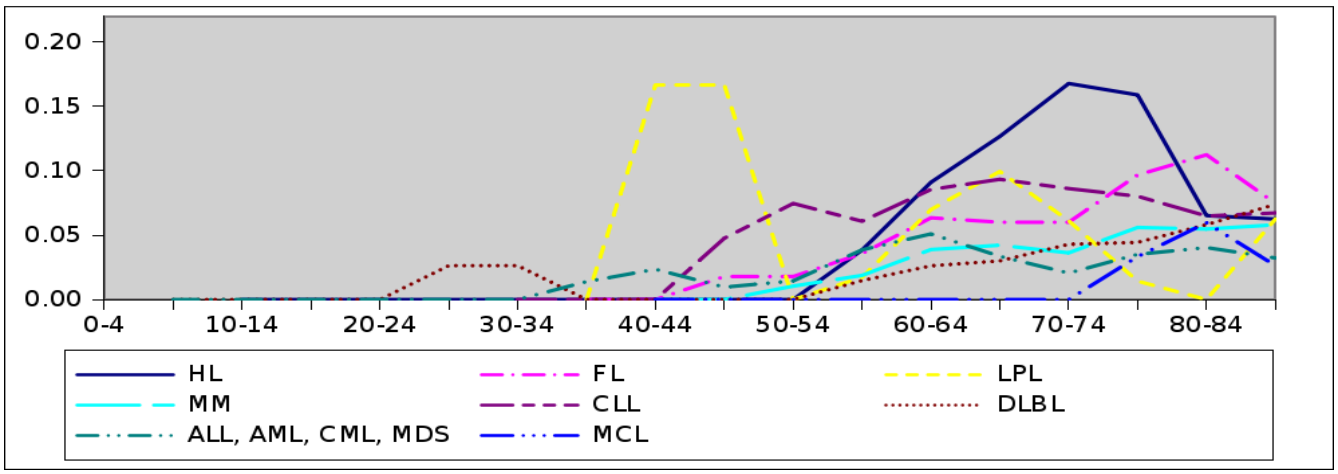
9.2.1 Cancer of breast

The following figures show the incidence rate curves of breast cancer associated with tumours of haematopoietic and lymphoid tissues (HL, MM, HPSCD, FL, CLL, MCL, LPL and DLBL) among women. The first part shows the incidence rate curves of breast cancer before and after lymphohaematopoietic cancers (before+after). The second part shows incidence rate curves of breast cancer before and one year after lymphohaematopoietic cancers (before+1 year). The last part shows the incidence rate curves of breast cancer before lymphohaematopoietic cancers (before) The x-axis shows the age of diagnosis of lymphohaematopoietic cancer in 5 year intervall age groups. The y-axis shows the incidence rate of cancer of breast in each age group.
The table after the figures show the individual data points of the figures.

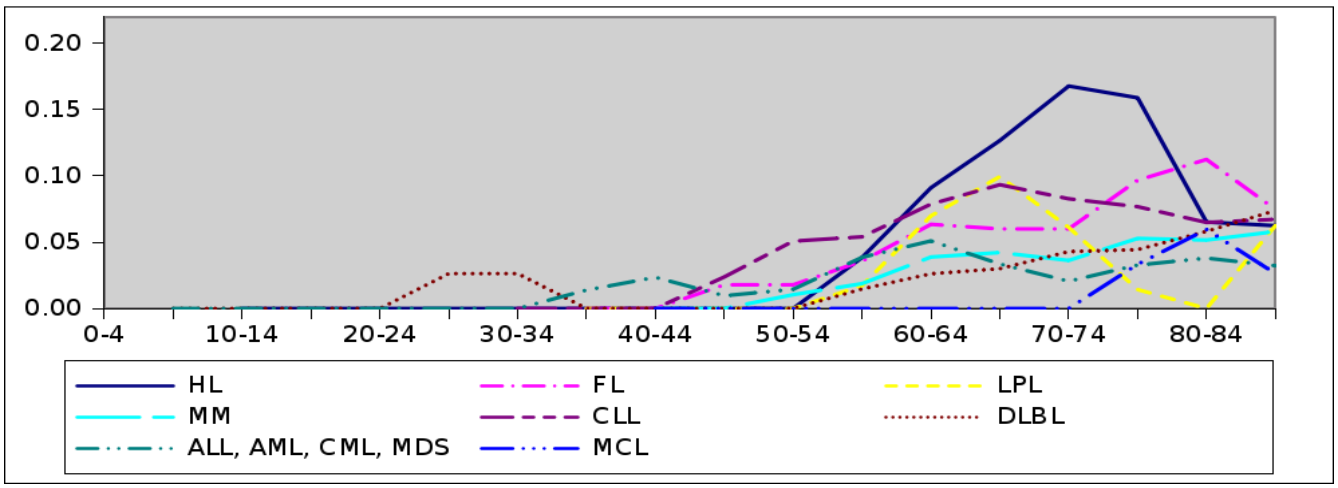
Cancer of breast (before and after)



Cancer of breast (before+1 year)



Cancer of breast (before)



(HPSCD: ALL, AML, CML and MDS)

Individual data points for breast cancers

name	age range	number of lymphoma	number of cancer of breast (before and after)	number of cancer of breast (before+1 year)	number of cancer of breast (before)
HL	0-4	0	0	0	0
	5-9	2	0	0	0
	10-14	15	0	0	0
	15-19	37	6	0	0
	20-24	62	5	0	0
	25-29	51	5	0	0
	30-34	56	4	0	0
	35-39	32	2	0	0
	40-44	31	3	0	0
	45-49	14	1	0	0
	50-54	18	1	0	0
	55-59	13	1	1	1
	60-64	19	4	2	2
	65-69	27	5	4	4
	70-74	16	3	3	3
	75-79	23	4	3	3
	80-84	13	0	0	0
	85-89	8	1	1	1
FL	0-4	0	0	0	0
	5-9	0	0	0	0
	10-14	0	0	0	0
	15-19	0	0	0	0
	20-24	1	0	0	0
	25-29	0	0	0	0
	30-34	3	0	0	0
	35-39	12	0	0	0
	40-44	17	1	0	0
	45-49	28	1	1	1
	50-54	44	1	0	0
	55-59	42	3	3	3
	60-64	36	2	2	2
	65-69	31	3	2	2
	70-74	36	2	2	2
	75-79	29	4	4	4
	80-84	23	2	2	2
	85-89	16	1	1	1
LPL	0-4	0	0	0	0
	5-9	0	0	0	0
	10-14	0	0	0	0

	15-19	0	0	0	0
	20-24	0	0	0	0
	25-29	0	0	0	0
	30-34	2	0	0	0
	35-39	1	0	0	0
	40-44	3	1	1	0
	45-49	5	0	0	0
LPL	50-54	13	0	0	0
	55-59	29	1	1	1
	60-64	19	3	2	2
	65-69	32	4	3	3
	70-74	35	1	1	1
	75-79	34	1	0	0
	80-84	31	0	0	0
	85-89	16	2	2	2
	0-4	0	0	0	0
	5-9	0	0	0	0
	10-14	0	0	0	0
	15-19	1	0	0	0
	20-24	0	0	0	0
	25-29	0	0	0	0
	30-34	0	0	0	0
	35-39	6	0	0	0
	40-44	18	0	0	0
MM	45-49	20	0	0	0
	50-54	48	2	1	1
	55-59	60	1	1	1
	60-64	82	5	5	5
	65-69	128	5	3	3
	70-74	163	11	8	8
	75-79	159	10	10	9
	80-84	150	8	7	7
	85-89	72	6	5	5
	0-4	0	0	0	0
	5-9	0	0	0	0
	10-14	0	0	0	0
	15-19	1	0	0	0
	20-24	0	0	0	0
CLL	25-29	3	0	0	0
	30-34	2	0	0	0
	35-39	11	1	0	0
	40-44	12	1	0	0
	45-49	21	2	2	1

CLL	50-54	37	2	2	2
	55-59	74	6	5	4
	60-64	87	14	9	9
	65-69	108	13	9	9
	70-74	146	14	13	12
	75-79	168	14	12	12
	80-84	137	10	8	8
	85-89	92	9	7	7
DLBL	0-4	1	0	0	0
	5-9	3	0	0	0
	10-14	1	0	0	0
	15-19	12	0	0	0
	20-24	12	0	0	0
	25-29	19	1	1	1
	30-34	25	0	0	0
	35-39	23	0	0	0
	40-44	29	0	0	0
	45-49	32	0	0	0
	50-54	42	0	0	0
	55-59	68	2	2	2
	60-64	87	5	2	2
	65-69	81	6	3	3
	70-74	123	6	6	6
	75-79	150	6	6	6
	80-84	131	10	10	10
	85-89	84	6	6	6
HPSCD: ALL, AML, CML, MDS	0-4	49	0	0	0
	5-9	32	0	0	0
	10-14	14	0	0	0
	15-19	14	0	0	0
	20-24	20	0	0	0
	25-29	25	0	0	0
	30-34	32	0	0	0
	35-39	36	2	1	1
	40-44	52	2	1	1
	45-49	51	0	0	0
	50-54	69	2	2	2
	55-59	83	6	4	4
	60-64	93	6	5	5
	65-69	150	3	2	2
	70-74	180	5	5	5
	75-79	212	9	9	8
	80-84	183	8	7	7

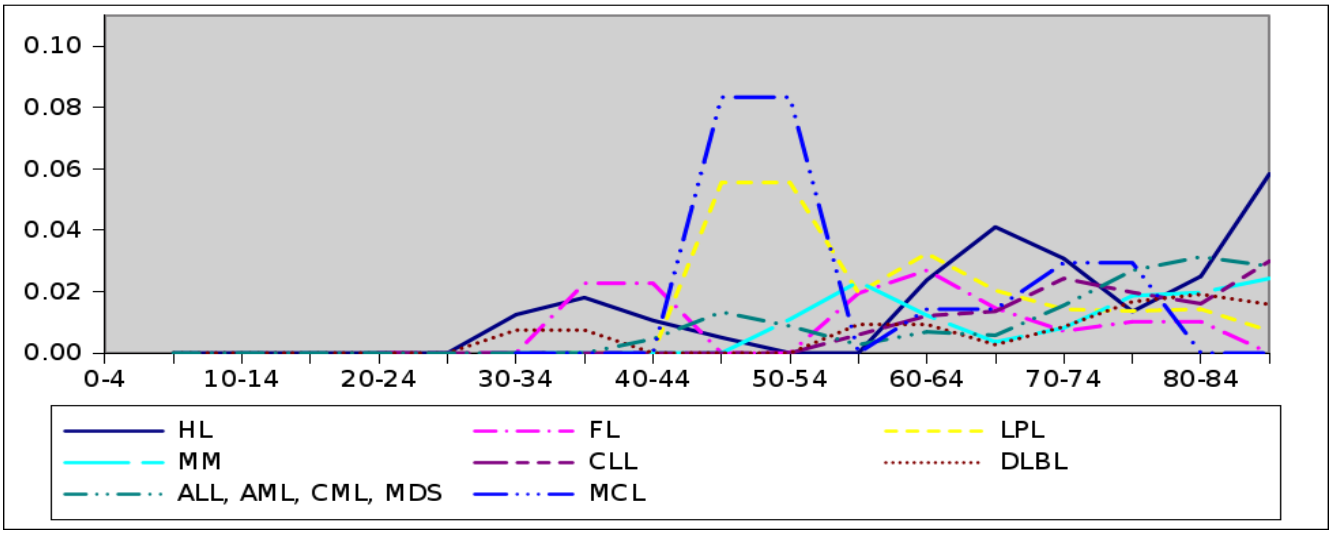
HPSCD	85-89	114	3	3	3
MCL	0-4	0	0	0	0
	5-9	0	0	0	0
	10-14	0	0	0	0
	15-19	0	0	0	0
	20-24	0	0	0	0
	25-29	1	0	0	0
	30-34	0	0	0	0
	35-39	1	0	0	0
	40-44	2	0	0	0
	45-49	1	0	0	0
	50-54	5	0	0	0
	55-59	6	0	0	0
	60-64	12	1	0	0
	65-69	13	1	0	0
	70-74	9	0	0	0
	75-79	15	1	1	1
	80-84	19	1	1	1
	85-89	7	0	0	0

9.2.2 Cancer of colon

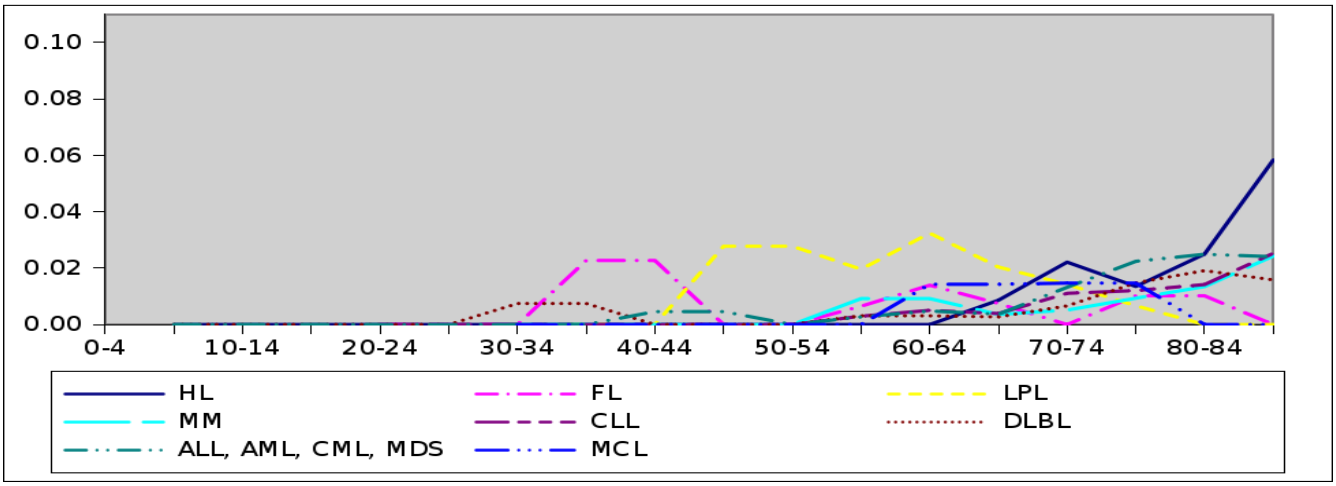
The following figures show the incidence rate curves of colon cancer associated with tumours of haematopoietic and lymphoid tissues among women and men. The first part shows the incidence rate curves of cancer of colon before and after lymphohaematopoietic cancers (before+after). The second part shows incidence rate curves of cancer of colon before and one year after lymphohaematopoietic cancers (before+1 year). The last part shows the incidence rate curves of cancer of colon before lymphohaematopoietic cancers (before). The x-axis shows the age of diagnosis of lymphohaematopoietic cancer in 5 year intervall age groups in years. The y-axis shows the incidence rates of cancer of colon in each age group.

The table after the figures show the individual data points of the figures.

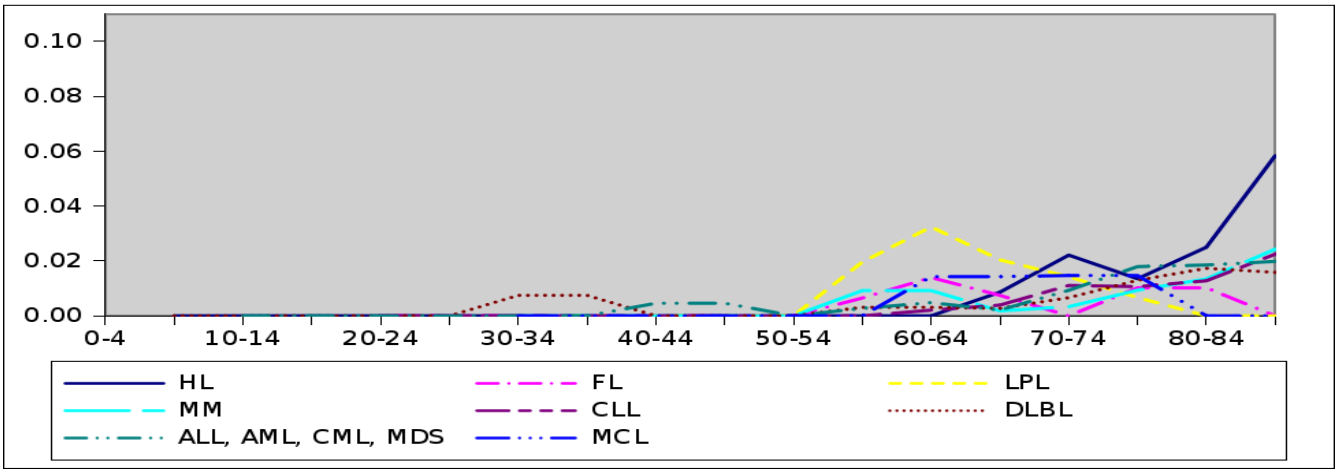
Cancer of colon, M+F (before and after)



Cancer of colon, M+F (before+1 year)

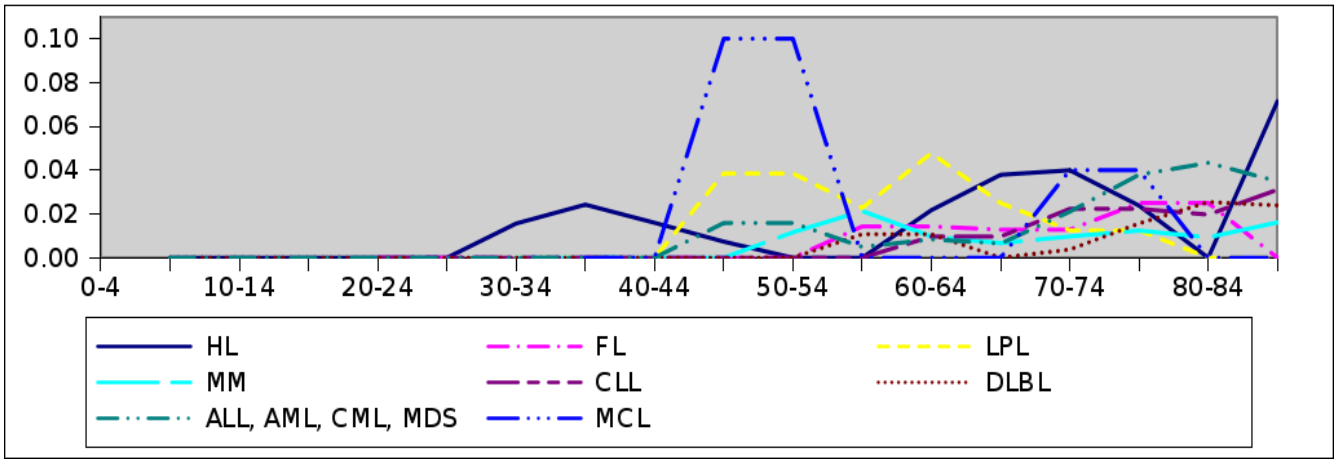


Cancer of colon, M+F (before)

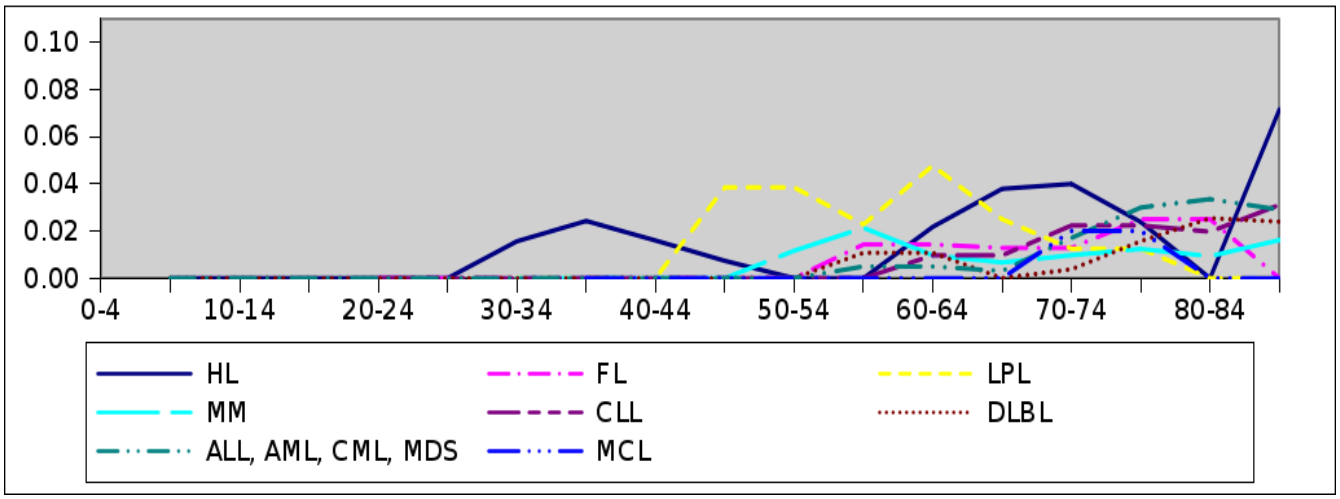


(HPSCD: ALL, AML, CML and MDS)

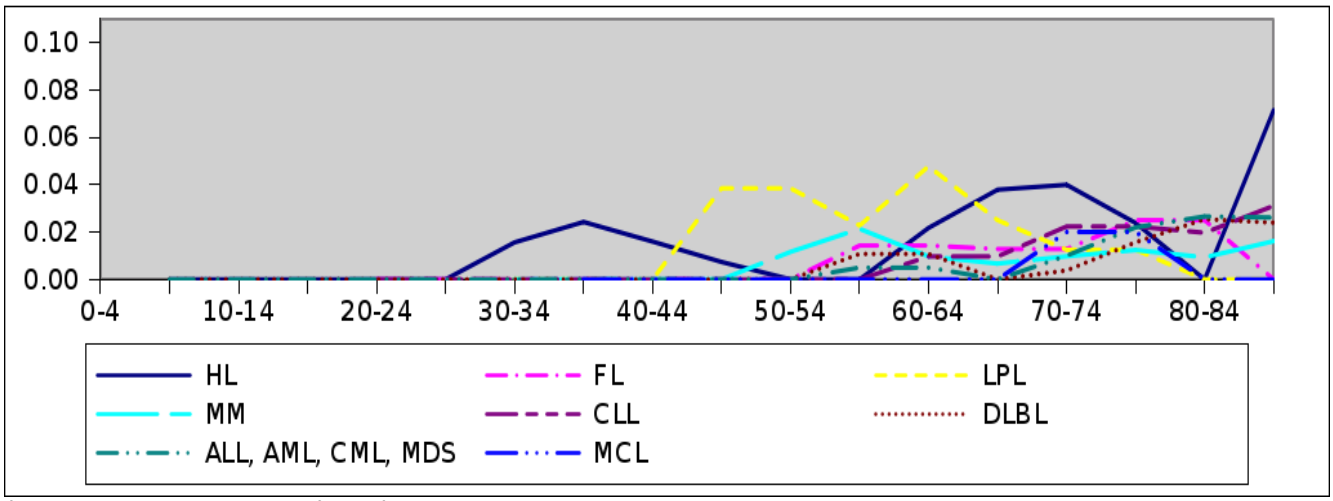
Cancer of colon, M (before and after)



Cancer of colon, M (before +1 year)

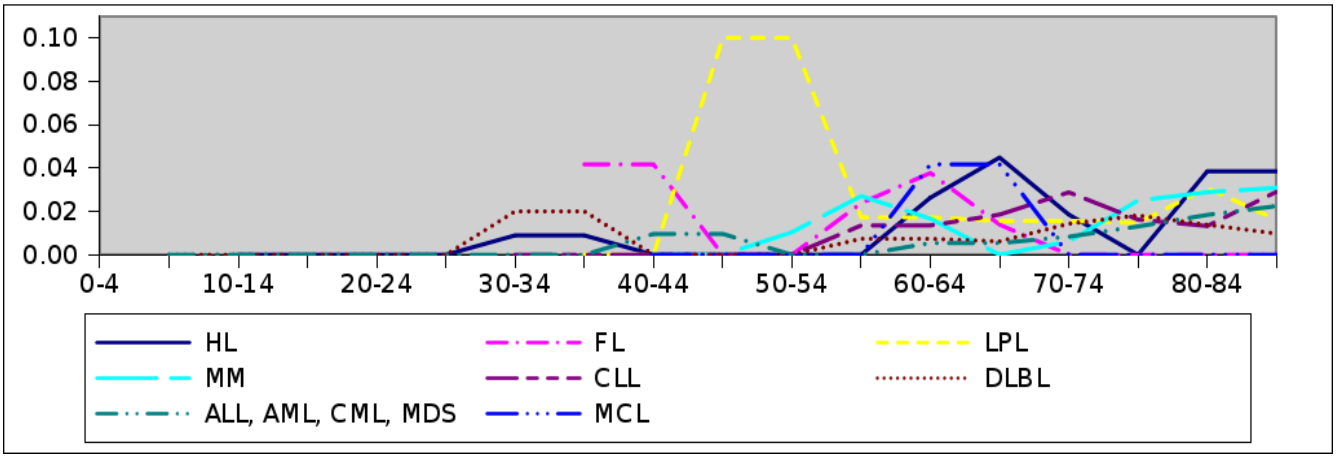


Cancer of colon, M (before)

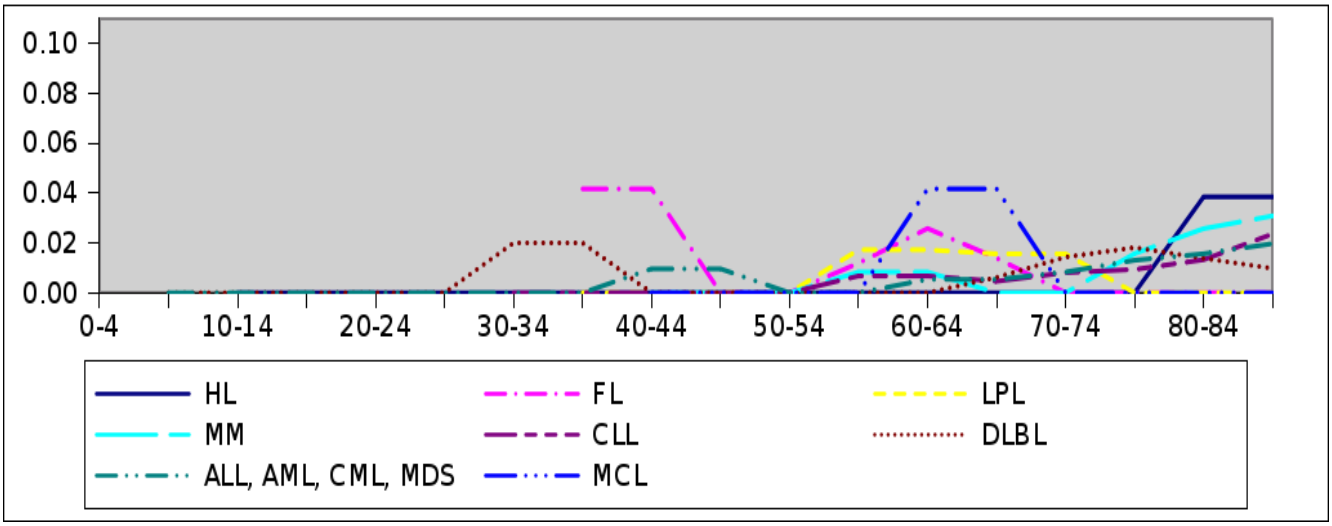


(HPSCD: ALL, AML, CML and MDS)

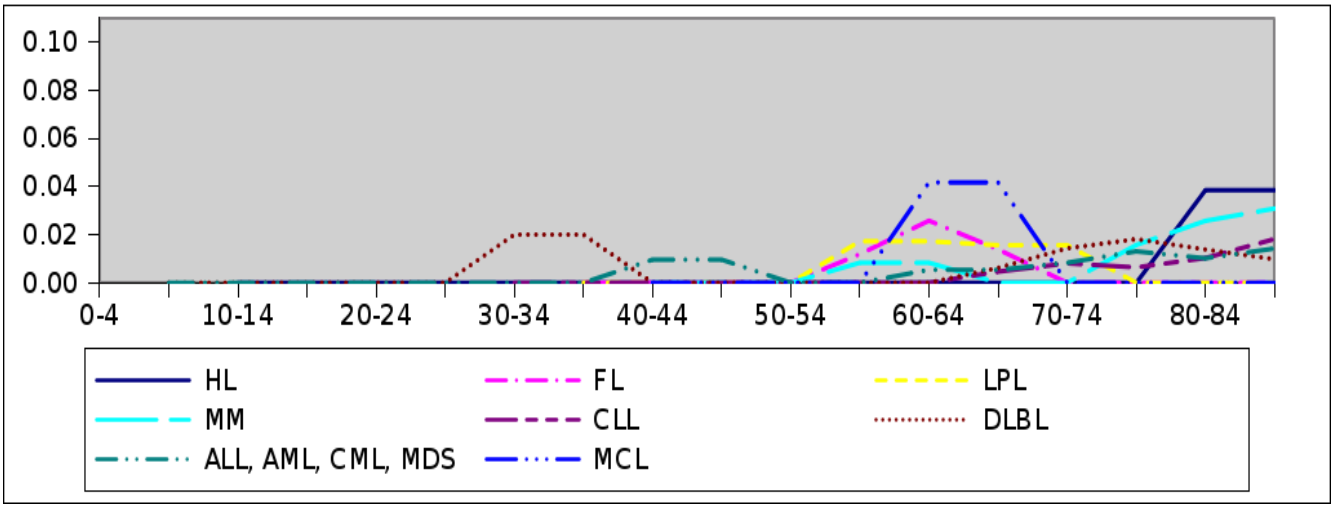
Cancer of colon, F (before and after)



Cancer of colon, F (before +1 year)



Cancer of colon, F (before)



(HPSCD: ALL, AML, CML and MDS)

Individual data points for colon cancer (N: number)

name	age range	N lympho haemat opoietic cancer	N colon cancer			N lympho haemat opoietic cancer	N colon cancer			N lympho haemat opoietic cancer	N colon cancer		
			before and after	before+ 1 year	before		before and after	before+ 1 year	before		before and after	before+1 year	before
		Total				M				F			
HL	0-4	1	0	0	0	1	0	0	0	0	0	0	0
	5-9	9	0	0	0	7	0	0	0	2	0	0	0
	10-14	30	0	0	0	15	0	0	0	15	0	0	0
	15-19	67	0	0	0	30	0	0	0	37	0	0	0
	20-24	125	0	0	0	63	0	0	0	62	0	0	0
	25-29	107	0	0	0	56	0	0	0	51	0	0	0
	30-34	120	3	0	0	64	2	0	0	56	1	0	0
	35-39	90	1	0	0	58	1	0	0	32	0	0	0
	40-44	99	1	0	0	68	1	0	0	31	0	0	0
	45-49	47	0	0	0	33	0	0	0	14	0	0	0
	50-54	55	0	0	0	37	0	0	0	18	0	0	0
	55-59	50	0	0	0	37	0	0	0	13	0	0	0
	60-64	42	2	0	0	23	1	0	0	19	1	0	0
	65-69	58	2	1	1	31	1	1	1	27	1	0	0
	70-74	37	1	1	1	21	1	1	1	16	0	0	0
	75-79	39	0	0	0	16	0	0	0	23	0	0	0
	80-84	20	1	1	1	7	0	0	0	13	1	1	1
	85-89	15	1	1	1	7	1	1	1	8	0	0	0
FL	0-4	0	0	0	0	0	0	0	0	0	0	0	0
	5-9	0	0	0	0	0	0	0	0	0	0	0	0
	10-14	0	0	0	0	0	0	0	0	0	0	0	0
	15-19	1	0	0	0	1	0	0	0	0	0	0	0
	20-24	2	0	0	0	1	0	0	0	1	0	0	0
	25-29	3	0	0	0	3	0	0	0	0	0	0	0
	30-34	8	0	0	0	5	0	0	0	3	0	0	0
	35-39	22	1	1	0	10	0	0	0	12	1	1	0
	40-44	31	0	0	0	14	0	0	0	17	0	0	0
	45-49	44	0	0	0	16	0	0	0	28	0	0	0
	50-54	78	0	0	0	34	0	0	0	44	0	0	0
	55-59	77	3	1	1	35	1	0	0	42	2	1	1
	60-64	67	1	1	1	31	0	0	0	36	1	1	1
	65-69	70	1	0	0	39	1	0	0	31	0	0	0
	70-74	57	0	0	0	21	0	0	0	36	0	0	0
	75-79	49	1	1	1	20	1	1	1	29	0	0	0
	80-84	35	0	0	0	12	0	0	0	23	0	0	0
	85-89	18	0	0	0	2	0	0	0	16	0	0	0
LPL	0-4	0	0	0	0	0	0	0	0	0	0	0	0
	5-9	0	0	0	0	0	0	0	0	0	0	0	0
	10-14	1	0	0	0	1	0	0	0	0	0	0	0

	15-19	0	0	0	0	0	0	0	0	0	0	0	0
	20-24	0	0	0	0	0	0	0	0	0	0	0	0
	25-29	2	0	0	0	2	0	0	0	0	0	0	0
	30-34	3	0	0	0	1	0	0	0	2	0	0	0
	35-39	3	0	0	0	2	0	0	0	1	0	0	0
	40-44	11	0	0	0	8	0	0	0	3	0	0	0
	45-49	18	2	1	0	13	1	1	0	5	1	0	0
LPL	50-54	31	0	0	0	18	0	0	0	13	0	0	0
	55-59	51	2	2	2	22	1	1	1	29	1	1	1
	60-64	39	1	1	1	20	1	1	1	19	0	0	0
	65-69	66	1	1	1	34	0	0	0	32	1	1	1
	70-74	75	1	1	1	40	1	1	1	35	0	0	0
	75-79	71	1	0	0	37	0	0	0	34	1	0	0
	80-84	69	1	0	0	38	0	0	0	31	1	0	0
	85-89	36	0	0	0	20	0	0	0	16	0	0	0
	0-4	0	0	0	0	0	0	0	0	0	0	0	0
	5-9	0	0	0	0	0	0	0	0	0	0	0	0
	10-14	0	0	0	0	0	0	0	0	0	0	0	0
	15-19	1	0	0	0	0	0	0	0	1	0	0	0
	20-24	0	0	0	0	0	0	0	0	0	0	0	0
	25-29	1	0	0	0	1	0	0	0	0	0	0	0
	30-34	2	0	0	0	2	0	0	0	0	0	0	0
	35-39	17	0	0	0	11	0	0	0	6	0	0	0
	40-44	45	0	0	0	27	0	0	0	18	0	0	0
MM	45-49	64	0	0	0	44	0	0	0	20	0	0	0
	50-54	91	2	0	0	43	1	0	0	48	1	0	0
	55-59	163	4	3	3	103	2	2	2	60	2	1	1
	60-64	194	0	0	0	112	0	0	0	82	0	0	0
	65-69	278	2	2	1	150	2	2	1	128	0	0	0
	70-74	326	3	1	1	163	1	1	1	163	2	0	0
	75-79	320	9	5	5	161	3	0	0	159	6	5	5
	80-84	266	3	3	3	116	0	0	0	150	3	3	3
	85-89	134	5	5	5	62	2	2	2	72	3	3	3
	0-4	0	0	0	0	0	0	0	0	0	0	0	0
	5-9	0	0	0	0	0	0	0	0	0	0	0	0
	10-14	0	0	0	0	0	0	0	0	0	0	0	0
	15-19	3	0	0	0	2	0	0	0	1	0	0	0
	20-24	2	0	0	0	2	0	0	0	0	0	0	0
	25-29	6	0	0	0	3	0	0	0	3	0	0	0
CLL	30-34	5	0	0	0	3	0	0	0	2	0	0	0
	35-39	23	0	0	0	12	0	0	0	11	0	0	0
	40-44	31	0	0	0	19	0	0	0	12	0	0	0
	45-49	53	0	0	0	32	0	0	0	21	0	0	0
	50-54	108	0	0	0	71	0	0	0	37	0	0	0
	55-59	168	2	1	0	94	0	0	0	74	2	1	0
	60-64	242	3	1	1	155	3	1	1	87	0	0	0

	65-69	271	4	1	1	163	0	0	0	108	4	1	1
	70-74	325	11	6	6	179	8	5	5	146	3	1	1
CLL	75-79	354	2	2	1	186	0	0	0	168	2	2	1
	80-84	264	7	6	6	127	5	4	4	137	2	2	2
	85-89	180	6	5	4	88	2	2	2	92	4	3	2
	0-4	2	0	0	0	1	0	0	0	1	0	0	0
	5-9	12	0	0	0	9	0	0	0	3	0	0	0
	10-14	4	0	0	0	3	0	0	0	1	0	0	0
	15-19	23	0	0	0	11	0	0	0	12	0	0	0
	20-24	24	0	0	0	12	0	0	0	12	0	0	0
	25-29	48	0	0	0	29	0	0	0	19	0	0	0
	30-34	67	1	1	1	42	0	0	0	25	1	1	1
	35-39	78	0	0	0	55	0	0	0	23	0	0	0
	40-44	78	0	0	0	49	0	0	0	29	0	0	0
DLBL	45-49	94	0	0	0	62	0	0	0	32	0	0	0
	50-54	120	0	0	0	78	0	0	0	42	0	0	0
	55-59	161	3	1	1	93	2	1	1	68	1	0	0
	60-64	178	0	0	0	91	0	0	0	87	0	0	0
	65-69	184	1	1	1	103	0	0	0	81	1	1	1
	70-74	256	3	2	2	133	1	0	0	123	2	2	2
	75-79	276	6	6	5	126	3	3	2	150	3	3	3
	80-84	242	4	4	4	111	3	3	3	131	1	1	1
	85-89	132	2	2	2	48	1	1	1	84	1	1	1
	0-4	134	0	0	0	85	0	0	0	49	0	0	0
	5-9	74	0	0	0	42	0	0	0	32	0	0	0
	10-14	49	0	0	0	35	0	0	0	14	0	0	0
	15-19	35	0	0	0	21	0	0	0	14	0	0	0
	20-24	59	0	0	0	39	0	0	0	20	0	0	0
	25-29	71	0	0	0	46	0	0	0	25	0	0	0
	30-34	62	0	0	0	30	0	0	0	32	0	0	0
	35-39	89	0	0	0	53	0	0	0	36	0	0	0
HPSCD: ALL, AML, CML, MDS	40-44	109	1	1	1	57	0	0	0	52	1	1	1
	45-49	114	2	0	0	63	2	0	0	51	0	0	0
	50-54	144	0	0	0	75	0	0	0	69	0	0	0
	55-59	184	1	1	1	101	1	1	1	83	0	0	0
	60-64	239	2	1	1	146	1	0	0	93	1	1	1
	65-69	314	1	1	0	164	1	1	0	150	0	0	0
	70-74	430	12	10	8	250	9	7	5	180	3	3	3
	75-79	463	12	10	8	251	10	8	6	212	2	2	2
	80-84	354	13	10	7	171	8	6	5	183	5	4	2
	85-89	201	4	4	4	87	2	2	2	114	2	2	2
	0-4	0	0	0	0	0	0	0	0	0	0	0	0
	5-9	0	0	0	0	0	0	0	0	0	0	0	0
MCL	10-14	0	0	0	0	0	0	0	0	0	0	0	0
	15-19	0	0	0	0	0	0	0	0	0	0	0	0
	20-24	0	0	0	0	0	0	0	0	0	0	0	0

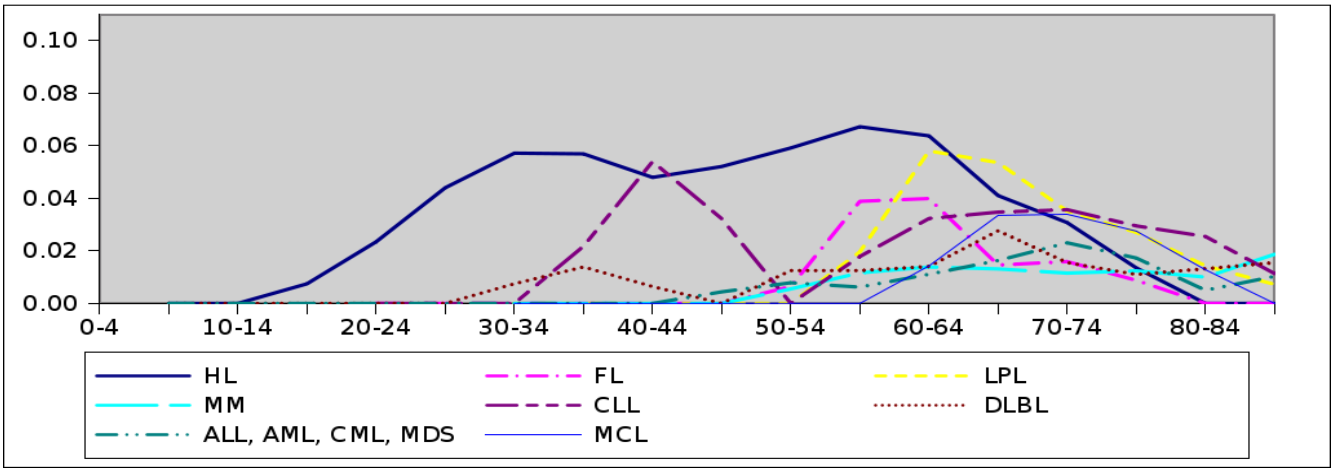
	25-29	1	0	0	0	0	0	0	0	1	0	0	0
	30-34	3	0	0	0	3	0	0	0	0	0	0	0
	35-39	5	0	0	0	4	0	0	0	1	0	0	0
	40-44	6	0	0	0	4	0	0	0	2	0	0	0
	45-49	6	1	0	0	5	1	0	0	1	0	0	0
	50-54	16	0	0	0	11	0	0	0	5	0	0	0
MCL	55-59	24	0	0	0	18	0	0	0	6	0	0	0
	60-64	35	1	1	1	23	0	0	0	12	1	1	1
	65-69	52	0	0	0	39	0	0	0	13	0	0	0
	70-74	34	2	1	1	25	2	1	1	9	0	0	0
	75-79	39	0	0	0	24	0	0	0	15	0	0	0
	80-84	34	0	0	0	15	0	0	0	19	0	0	0
	85-89	10	0	0	0	3	0	0	0	7	0	0	0

9.2.3 Cancer of lung

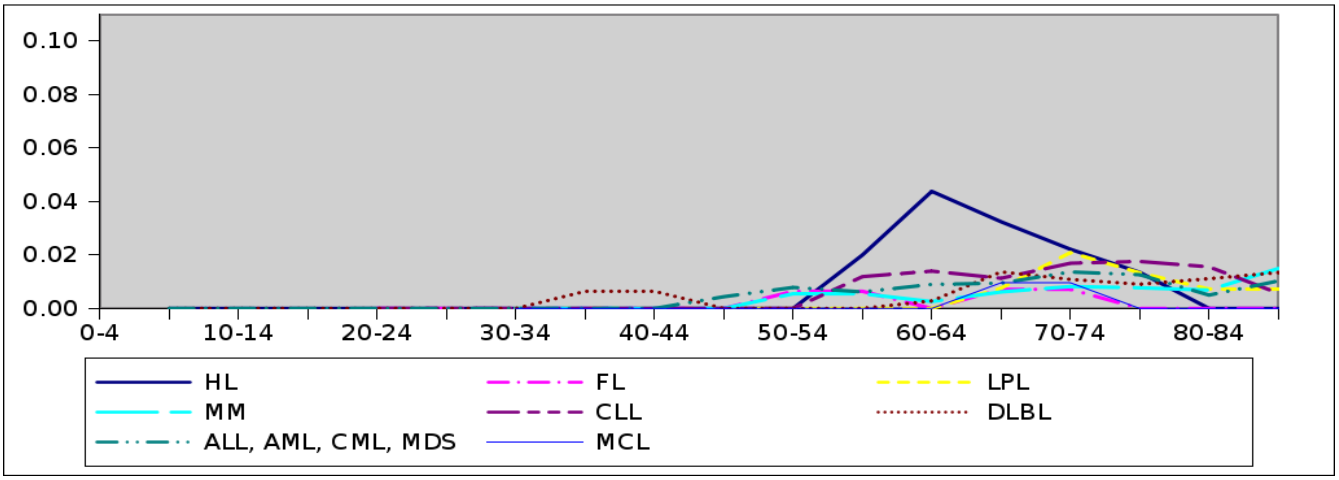
The following figures show the incidence rate curves of lung cancer associated with tumours of haematopoietic and lymphoid tissues among women and men. The first part shows the incidence rate curves of cancer of lung before and after lymphohaematopoietic cancers (before+after). The second part shows incidence rate curves of cancer of lung before and one year after lymphohaematopoietic cancers (before+1 year). The last part shows the incidence rate curves of cancer of lung before lymphohaematopoietic cancers (before). The x-axis shows the age of diagnosis of lymphohaematopoietic cancer in 5 year intervall age groups in years. The y-axis shows the incidence rates of cancer of lung in each age group.

The table after the figures show the individual data points of the figures.

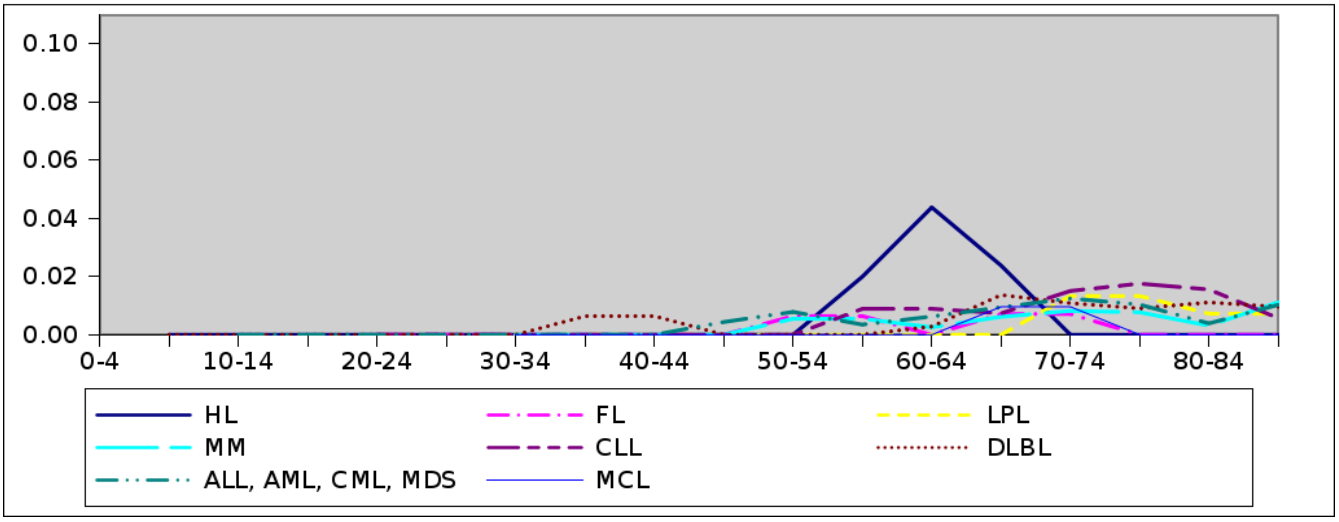
Cancer of bronchus and lung, M+F (before and after)



Cancer of bronchus and lung, M+F (before+1 year)

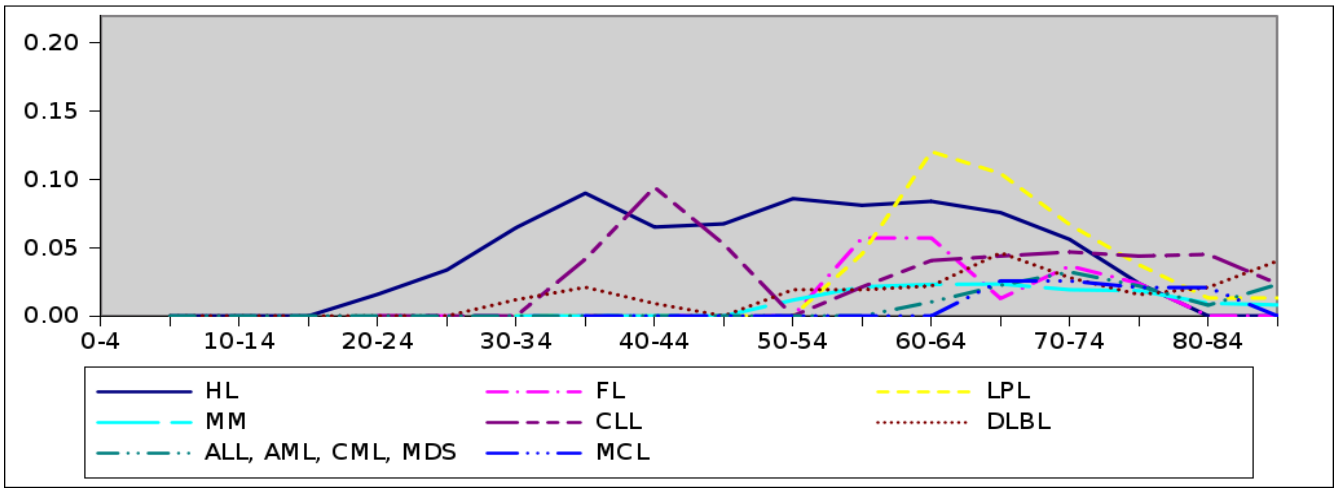


Cancer of bronchus and lung, M+F (before)

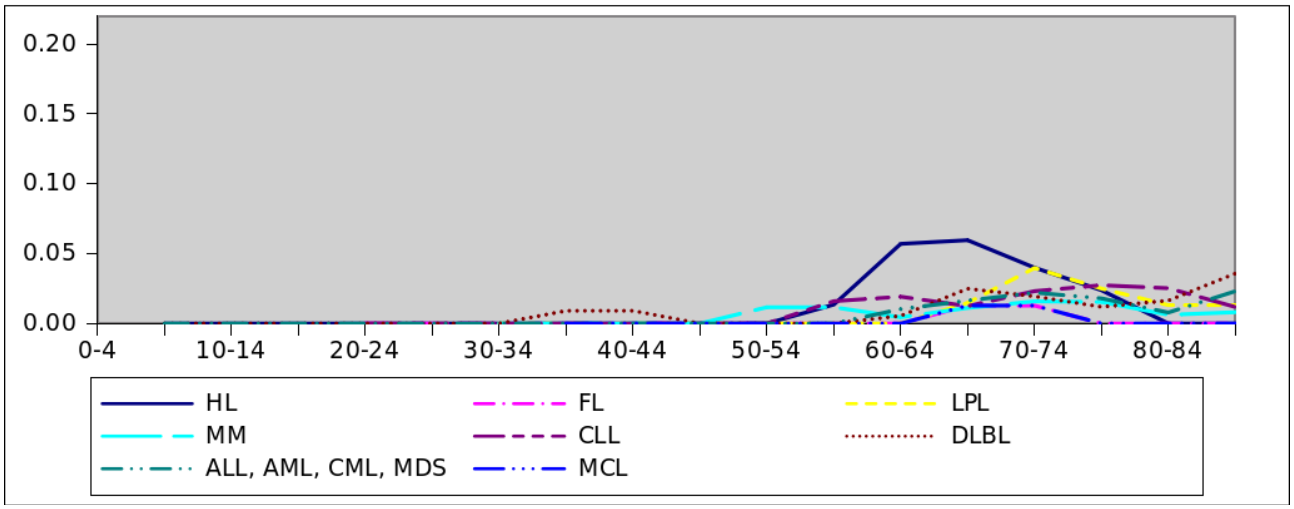


(HPSCD: ALL, AML, CML and MDS)

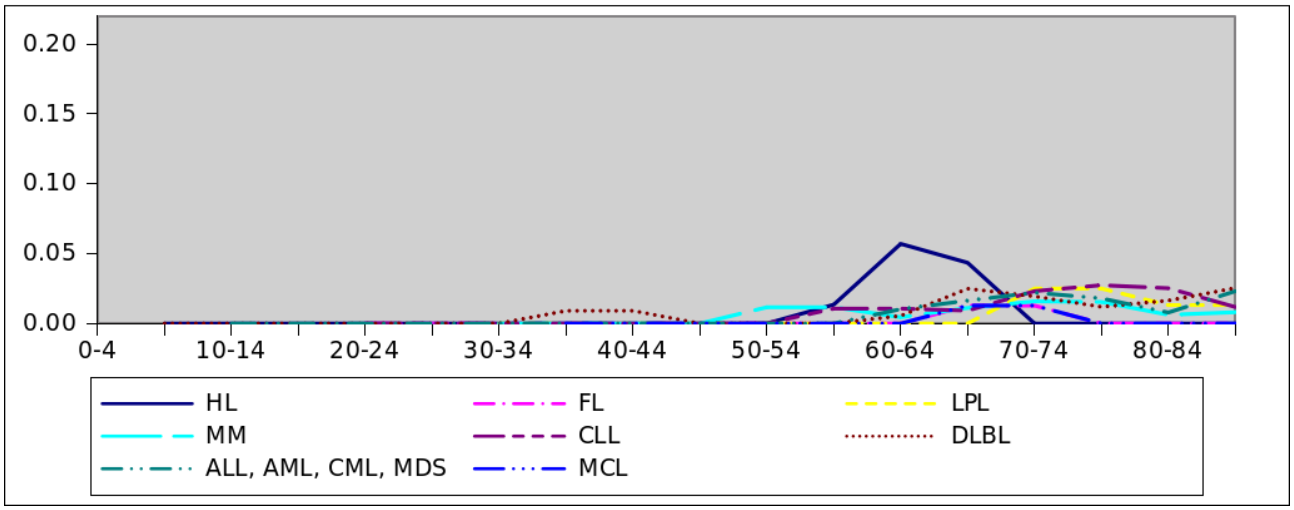
Cancer of bronchus and lung, M (before and after)



Cancer of bronchus and lung, M (before +1 year)

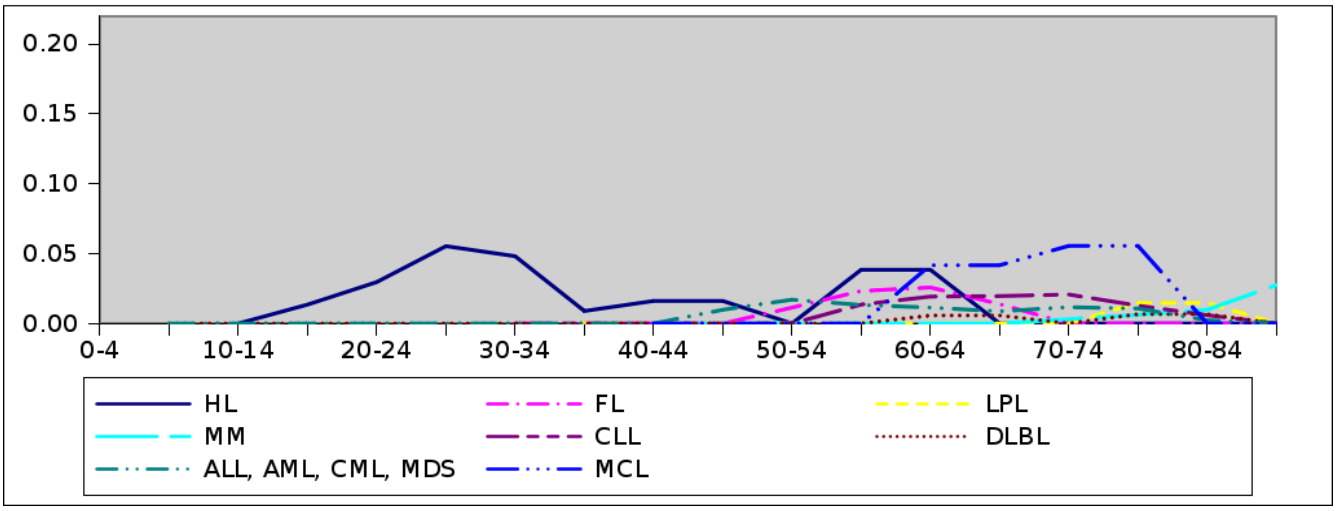


Cancer of bronchus and lung, M (before)

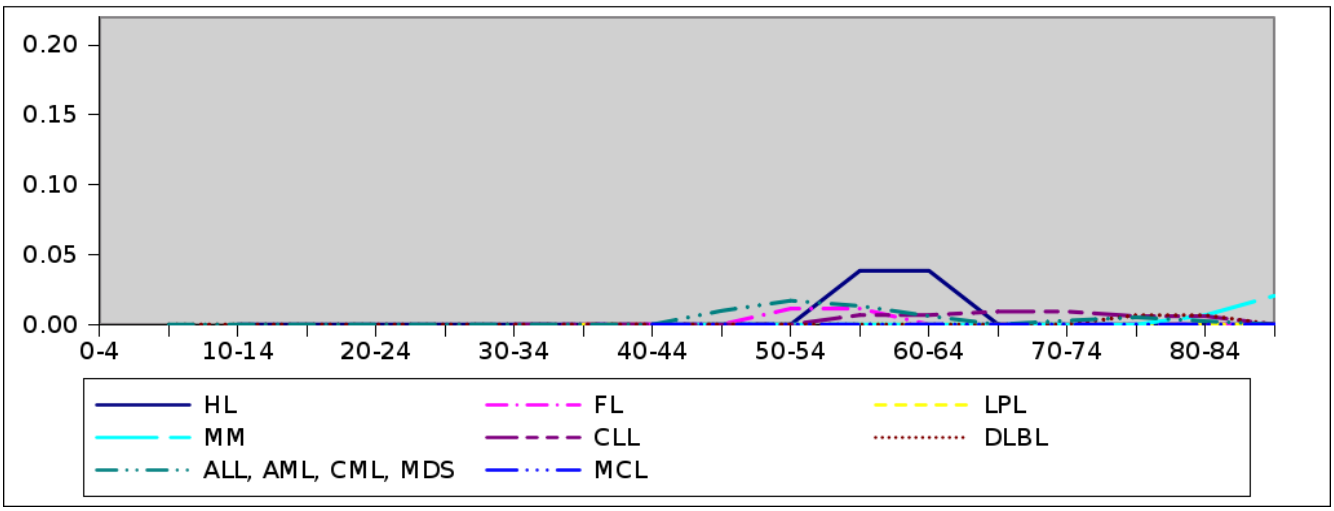


(HPSCD: ALL, AML, CML and MDS)

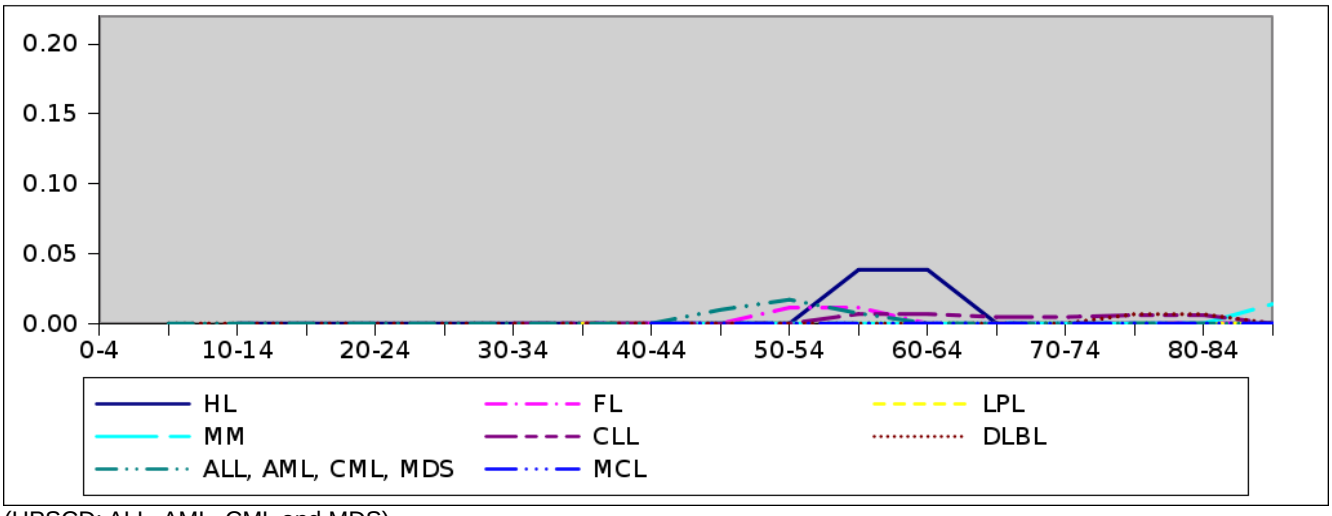
Cancer of bronchus and lung, F (before and after)



Cancer of bronchus and lung, F (before +1 year)



Cancer of bronchus and lung, F (before)



(HPSCD: ALL, AML, CML and MDS)

individual data points for lung cancer (N: numbers)

name	age range	N lympho haemat opoietic cancer	N lung cancer			N lympho haemat opoietic cancer	N lung cancer			N lympho haemat opoietic cancer	N lung cancer		
			before and after	before+ 1 year	before		before and after	before+ 1 year	before		before and after	before+ 1 year	before
		Total				M				F			
HL	0-4	1	0	0	0	1	0	0	0	0	0	0	0
	5-9	9	0	0	0	7	0	0	0	2	0	0	0
	10-14	30	0	0	0	15	0	0	0	15	0	0	0
	15-19	67	1	0	0	30	0	0	0	37	1	0	0
	20-24	125	4	0	0	63	2	0	0	62	2	0	0
	25-29	107	6	0	0	56	2	0	0	51	4	0	0
	30-34	120	7	0	0	64	6	0	0	56	1	0	0
	35-39	90	5	0	0	58	5	0	0	32	0	0	0
	40-44	99	4	0	0	68	3	0	0	31	1	0	0
	45-49	47	3	0	0	33	3	0	0	14	0	0	0
	50-54	55	3	0	0	37	3	0	0	18	0	0	0
	55-59	50	4	2	2	37	3	1	1	13	1	1	1
	60-64	42	2	2	2	23	2	2	2	19	0	0	0
	65-69	58	2	1	0	31	2	1	0	27	0	0	0
	70-74	37	1	1	0	21	1	1	0	16	0	0	0
	75-79	39	0	0	0	16	0	0	0	23	0	0	0
	80-84	20	0	0	0	7	0	0	0	13	0	0	0
	85-89	15	0	0	0	7	0	0	0	8	0	0	0
FL	0-4	0	0	0	0	0	0	0	0	0	0	0	0
	5-9	0	0	0	0	0	0	0	0	0	0	0	0
	10-14	0	0	0	0	0	0	0	0	0	0	0	0
	15-19	1	0	0	0	1	0	0	0	0	0	0	0
	20-24	2	0	0	0	1	0	0	0	1	0	0	0
	25-29	3	0	0	0	3	0	0	0	0	0	0	0
	30-34	8	0	0	0	5	0	0	0	3	0	0	0
	35-39	22	0	0	0	10	0	0	0	12	0	0	0
	40-44	31	0	0	0	14	0	0	0	17	0	0	0
	45-49	44	0	0	0	16	0	0	0	28	0	0	0
	50-54	78	1	1	1	34	0	0	0	44	1	1	1
	55-59	77	5	0	0	35	4	0	0	42	1	0	0
	60-64	67	1	0	0	31	0	0	0	36	1	0	0
	65-69	70	1	1	1	39	1	1	1	31	0	0	0
	70-74	57	1	0	0	21	1	0	0	36	0	0	0
	75-79	49	0	0	0	20	0	0	0	29	0	0	0
	80-84	35	0	0	0	12	0	0	0	23	0	0	0
	85-89	18	0	0	0	2	0	0	0	16	0	0	0
LPL	0-4	0	0	0	0	0	0	0	0	0	0	0	0
	5-9	0	0	0	0	0	0	0	0	0	0	0	0
	10-14	1	0	0	0	1	0	0	0	0	0	0	0

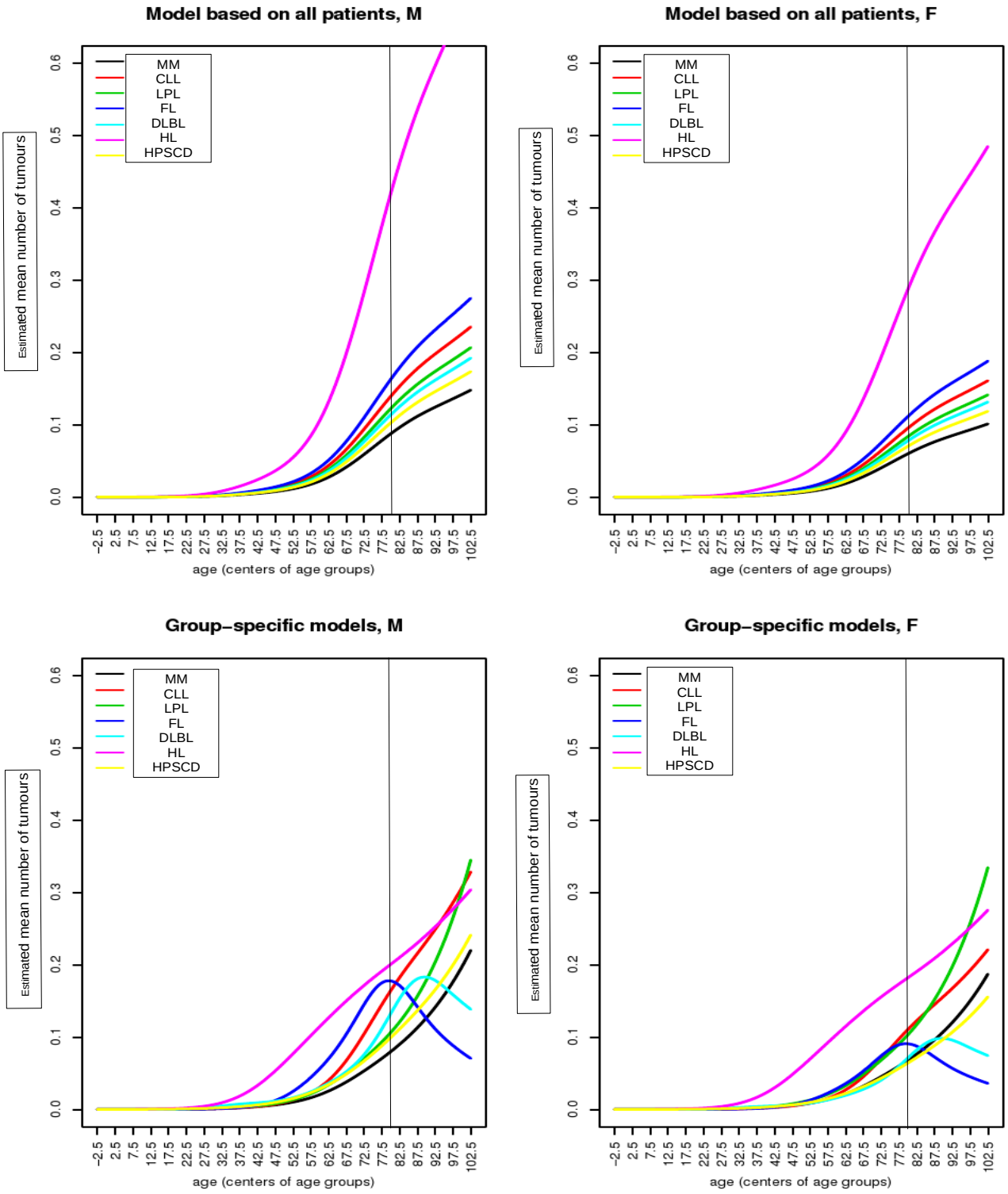
LPL	15-19	0	0	0	0	0	0	0	0	0	0	0	0
	20-24	0	0	0	0	0	0	0	0	0	0	0	0
	25-29	2	0	0	0	2	0	0	0	0	0	0	0
	30-34	3	0	0	0	1	0	0	0	2	0	0	0
	35-39	3	0	0	0	2	0	0	0	1	0	0	0
	40-44	11	0	0	0	8	0	0	0	3	0	0	0
	45-49	18	0	0	0	13	0	0	0	5	0	0	0
	50-54	31	0	0	0	18	0	0	0	13	0	0	0
	55-59	51	2	0	0	22	2	0	0	29	0	0	0
	60-64	39	3	0	0	20	3	0	0	19	0	0	0
	65-69	66	2	1	0	34	2	1	0	32	0	0	0
	70-74	75	3	2	2	40	3	2	2	35	0	0	0
	75-79	71	1	0	0	37	0	0	0	34	1	0	0
	80-84	69	1	1	1	38	1	1	1	31	0	0	0
	85-89	36	0	0	0	20	0	0	0	16	0	0	0
MM	0-4	0	0	0	0	0	0	0	0	0	0	0	0
	5-9	0	0	0	0	0	0	0	0	0	0	0	0
	10-14	0	0	0	0	0	0	0	0	0	0	0	0
	15-19	1	0	0	0	0	0	0	0	1	0	0	0
	20-24	0	0	0	0	0	0	0	0	0	0	0	0
	25-29	1	0	0	0	1	0	0	0	0	0	0	0
	30-34	2	0	0	0	2	0	0	0	0	0	0	0
	35-39	17	0	0	0	11	0	0	0	6	0	0	0
	40-44	45	0	0	0	27	0	0	0	18	0	0	0
	45-49	64	0	0	0	44	0	0	0	20	0	0	0
	50-54	91	1	1	1	43	1	1	1	48	0	0	0
	55-59	163	2	0	0	103	2	0	0	60	0	0	0
	60-64	194	3	1	1	112	3	1	1	82	0	0	0
	65-69	278	3	2	2	150	3	2	2	128	0	0	0
	70-74	326	4	3	3	163	3	3	3	163	1	0	0
	75-79	320	4	2	2	161	3	2	2	159	1	0	0
	80-84	266	2	2	0	116	0	0	0	150	2	2	0
	85-89	134	4	3	3	62	1	1	1	72	3	2	2
CLL	0-4	0	0	0	0	0	0	0	0	0	0	0	0
	5-9	0	0	0	0	0	0	0	0	0	0	0	0
	10-14	0	0	0	0	0	0	0	0	0	0	0	0
	15-19	3	0	0	0	2	0	0	0	1	0	0	0
	20-24	2	0	0	0	2	0	0	0	0	0	0	0
	25-29	6	0	0	0	3	0	0	0	3	0	0	0
	30-34	5	0	0	0	3	0	0	0	2	0	0	0
	35-39	23	1	0	0	12	1	0	0	11	0	0	0
	40-44	31	2	0	0	19	2	0	0	12	0	0	0
	45-49	53	0	0	0	32	0	0	0	21	0	0	0
	50-54	108	0	0	0	71	0	0	0	37	0	0	0
	55-59	168	6	4	3	94	4	3	2	74	2	1	1
	60-64	242	7	1	0	155	6	1	0	87	1	0	0

CLL	65-69	271	11	5	4	163	8	3	3	108	3	2	1
	70-74	325	10	5	5	179	8	5	5	146	2	0	0
	75-79	354	10	7	7	186	8	5	5	168	2	2	2
	80-84	264	6	3	3	127	6	3	3	137	0	0	0
	85-89	180	0	0	0	88	0	0	0	92	0	0	0
DLBL	0-4	2	0	0	0	1	0	0	0	1	0	0	0
	5-9	12	0	0	0	9	0	0	0	3	0	0	0
	10-14	4	0	0	0	3	0	0	0	1	0	0	0
	15-19	23	0	0	0	11	0	0	0	12	0	0	0
	20-24	24	0	0	0	12	0	0	0	12	0	0	0
	25-29	48	0	0	0	29	0	0	0	19	0	0	0
	30-34	67	1	0	0	42	1	0	0	25	0	0	0
	35-39	78	1	1	1	55	1	1	1	23	0	0	0
	40-44	78	0	0	0	49	0	0	0	29	0	0	0
	45-49	94	0	0	0	62	0	0	0	32	0	0	0
	50-54	120	3	0	0	78	3	0	0	42	0	0	0
	55-59	161	0	0	0	93	0	0	0	68	0	0	0
	60-64	178	5	1	1	91	4	1	1	87	1	0	0
	65-69	184	5	4	4	103	5	4	4	81	0	0	0
	70-74	256	1	0	0	133	1	0	0	123	0	0	0
	75-79	276	5	5	5	126	3	3	3	150	2	2	2
	80-84	242	2	1	1	111	2	1	1	131	0	0	0
	85-89	132	3	3	2	48	3	3	2	84	0	0	0
HPSCD: ALL, AML, CML, MDS	0-4	134	0	0	0	85	0	0	0	49	0	0	0
	5-9	74	0	0	0	42	0	0	0	32	0	0	0
	10-14	49	0	0	0	35	0	0	0	14	0	0	0
	15-19	35	0	0	0	21	0	0	0	14	0	0	0
	20-24	59	0	0	0	39	0	0	0	20	0	0	0
	25-29	71	0	0	0	46	0	0	0	25	0	0	0
	30-34	62	0	0	0	30	0	0	0	32	0	0	0
	35-39	89	0	0	0	53	0	0	0	36	0	0	0
	40-44	109	0	0	0	57	0	0	0	52	0	0	0
	45-49	114	1	1	1	63	0	0	0	51	1	1	1
	50-54	144	1	1	1	75	0	0	0	69	1	1	1
	55-59	184	1	1	0	101	0	0	0	83	1	1	0
	60-64	239	4	3	3	146	3	3	3	93	1	0	0
	65-69	314	5	2	2	164	4	2	2	150	1	0	0
	70-74	430	13	9	8	250	10	8	8	180	3	1	0
	75-79	463	2	2	1	251	1	1	1	212	1	1	0
	80-84	354	2	2	2	171	2	2	2	183	0	0	0
	85-89	201	3	3	3	87	3	3	3	114	0	0	0
MCL	0-4	0	0	0	0	0	0	0	0	0	0	0	o
	5-9	0	0	0	0	0	0	0	0	0	0	0	o
	10-14	0	0	0	0	0	0	0	0	0	0		
MCL	15-19	0	0	0	0	0	0	0	0	0	0	0	o
	20-24	0	0	0	0	0	0	0	0	0	0	0	o

25-29	1	0	0	0	0	0	0	0	1	0	0	o
30-34	3	0	0	0	3	0	0	0	0	0	0	o
35-39	5	0	0	0	4	0	0	0	1	0	0	o
40-44	6	0	0	0	4	0	0	0	2	0	0	o
45-49	6	0	0	0	5	0	0	0	1	0	0	o
50-54	16	0	0	0	11	0	0	0	5	0	0	o
55-59	24	0	0	0	18	0	0	0	6	0	0	o
60-64	35	1	0	0	23	0	0	0	12	1	0	o
65-69	52	2	1	1	39	2	1	1	13	0	0	o
70-74	34	1	0	0	25	0	0	0	9	1	0	o
75-79	39	1	0	0	24	1	0	0	15	0	0	o
80-84	34	0	0	0	15	0	0	0	19	0	0	o
85-89	10	0	0	0	3	0	0	0	7	0		

9.3 Statistical analyses for expected numbers of associated cancers before and after tumour of haematopoietic and lymphoid tissues

The next figure analyses the estimated number of AMN before and after the lymphohaematopoietic cancer with a generalized additive model (GAM) for Poisson regression. AMN rates were calculated as events per unit time of age group of diagnosis of lymphohaematopoietic cancer.



Estimated mean numbers of associated cancers before and after tumour of haematopoietic and lymphoid tissues: joint model curves (top) and group specific curves (botttom) among women (right) and among men (left) [48]

10 Curriculum vitae

Géraldine Monique Bard von Genf GE

01.10.1978	Geboren in Genf (GE)
1986-92	Primarschule in Grand-Saconnex (GE)
1993-97	Collège Rousseau, Genf (Matura Typ C)
1998-2004	Medizinstudium in Genf
01/2004	Staatsexamen an der Universität Genf
2004-2006	Assistenzärztin, je ein Jahr Chirurgie und Innere im Hôpital de Saint-Loup (VD)
2006-2007	Assistenzärztin, Orthopädie im Kantonsspital Bruderholz (BL)
2008-2010	Assistenzärztin, Innere Medizin im Kantonsspital Bruderholz (BL)
2010	FMH-Prüfung, Innere Medizin
ab 2011	Hausärztin, Centramed Gesundheitszentrum Riehen (BS)